

HUMAN
EMBRYOLOGY

BOOKS BY BRADLEY M. PATTEN

Human Embryology

Early Embryology of the Chick

Embryology of the Pig

HUMAN EMBRYOLOGY

By
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*Professor of Anatomy in the
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WITH 1366 DRAWINGS AND PHOTOGRAPHS
GROUPED AS 446 ILLUSTRATIONS
53 IN COLOR



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Dedicated to My Father

WILLIAM PATTEN

Late Professor of Biology in Dartmouth College
whose devotion to research, scientific achievements,
and rich human understanding have
been a never-ending source of inspiration

Preface

This book represents an endeavor to set forth in simple and readable form the phases of human embryology which are of especial interest to medical students and physicians. The heaviness of the scholastic demands on our medical students makes it imperative that a book for their use be held within reasonable compass. It has, therefore, seemed expedient to omit much of the comparative and theoretical material that has traditionally been included in embryological texts, especially as such aspects of the subject are being increasingly well covered by most students in their premedical training.

Special thought has been devoted to developing those aspects of embryology which are of importance as a background in other medical subjects. The very early stages in the formation of the embryo, the mechanism of its implantation in the uterus, and the correlated changes in the reproductive organs of the mother, which are so important in connection with gynecology and obstetrics, have received special attention. Other things which have been emphasized are the more advanced stages in the formation of the organ systems which are so helpful in understanding the plan of the body as it is seen in gross anatomy, and the histogenesis of some of the major organs, a knowledge of which aids so greatly in dealing with their architecture as it is encountered in microscopical anatomy. Because of their clinical importance, an especially careful endeavor has been made to cover adequately the more frequently occurring developmental anomalies.

Throughout the text every effort has been made to present developmental processes, not as a series of still pictures of selected stages but as a story of dynamic events, with the emphasis on their sequence and significance. Since undiluted descriptive matter is assimilated with difficulty and precariously retained, sections interpreting the functional significance of the relations involved have been interspersed freely with the descriptions of developmental morphology. This lengthens the text somewhat but it should, nevertheless, lighten the work of the student by helping him to use a chain of correlations to hold together his newly acquired information rather than relying on mere memory. The functional correlations have been especially emphasized in dealing with the nervous and circulatory systems. These two systems, one as co-ordinator and the other as purveyor, are so intimately interrelated with all the other systems in the body that their structural plan has little meaning unless it is interpreted from the functional standpoint.

ACKNOWLEDGMENTS

has given his approval to my use of several of his own figures and to the use of a large number of embryological drawings which we had previously published in collaboration in Curtis' "*Obstetrics and Gynecology*" Dr Bartelmez generously sent me a number of his original photomicrographs which were used directly in assembling some of the figures on uterine changes Drs Hertig and Rock have allowed me to utilize freely their extraordinarily interesting studies on newly implanted human embryos

I wish I might acknowledge individually the help that I have received from many students over a period of many years The ideals, the earnestness, and the willingness to give of their best exhibited by the medical students it has been my privilege to teach has been an inspiration to give back to them the very best that I could in the way of a book for their use Help from students has, also, taken more tangible forms Many reconstructions I have utilized directly or indirectly have been made by students who wanted to go beyond the minimum requirements Some of the illustrations have utilized the work of students, notably the beautiful drawings of the developing skeletal system done by Dr Jane Schaefer while she was a first-year medical student Of even greater assistance have been students' suggestions during the development of the work As each year's new group of figures began to take shape they were laid out in the laboratory for the use and criticism of the then current class Their constructive suggestions as to where clearer delineation or additional labeling was needed have contributed much to the usefulness of the illustrations Various sections of the book, while still in manuscript form, were read by students and their frank pointing out of passages that were obscure has given assistance of a type that could not come as effectively from any other source

My secretary, Mrs Dorothy Hargis, has prepared much of the final copy and her unusually accurate typing and critical proofreading have averted many errors

From the incipience of the work The Blakiston Company has given me the most generous co-operation Many persons have been so helpful that it is difficult to single out specific incidents I can not, however, omit a personal acknowledgment to Mr Willard T Shoener He arranged for the proofing of the illustrations in small groups so that as the work progressed the early shortcomings in drawing technic could be eliminated His personal interest in the shaping of the book and his advice on the technical problems involved have been invaluable

To my wife I owe the greatest debt of all For many years she has cheerfully given what were supposed to be our vacations to typing scissor-edited and deviously interlined longhand manuscript that no one less familiar with my handwriting and the vagaries of my spelling could have put in serviceable form Without her assistance and her encouragement through periods of lagging progress, the completion of the book would have been long delayed

BRADLEY M PATTEN

Contents

1 Introduction	
Development of Embryology as a Science	1
Embryology as a Subject in the Medical Curriculum	5
Necessity of Laboratory Study	6
2 Reproductive Organs, Gametogenesis	
Reproductive Organs	8
Gametogenesis	11
Ovulation	24
Corpus Luteum	25
3 Sexual Cycle and Fertilization	
Sexual Cycle	38
Fertilization	52
Sex Determination	56
4 Cleavage, Germ Layers, and Establishment of Embryonic Body	
Cleavage	59
Differentiation of Blastodermic Vesicle	62
Formation of Germ Layers	65
Formation of Notochord	68
Structure of Young Human Embryos	75
5 Early Differentiation of the Body and Establishing of Organ Systems	
Primitive Streak as a Growth Center	85
Early Differentiation of Cephalic Region	87
Early Differentiation in Trunk Region	92
Early Differentiation of Mesoderm	97
Nervous System	105
Digestive System	117
Urogenital System	122
Coelom	123
Circulatory System	125
6 Fetal Membranes and Placenta	
Formation and Primary Relations of Fetal Membranes	139
Human Fetal-Maternal Relations	145

Birth and the "After-birth"	167
Hormonal Regulatory Actions During Pregnancy	170
Anomalies of Fetal-Maternal Relations	173
7 Age, Growth, and Changes in External Form of Body	
Estimation of Age and Methods of Measuring Embryos	181
Growth of Body as a Whole	183
Development of External Form of Body	189
Growth of Organ Systems	198
8 Twins, Double Monsters and Teratology	
Twins	204
Frequency of Multiple Births	205
Double Monsters	209
Embryomata and Teratomata	217
Teratology	219
Gigantism and Acromegaly	224
Dwarfism	224
Causative Factors in Abnormal Development	227
9 Integumentary System	
The Skin	233
Nails and Hair	235
Glands of the Skin	239
Developmental Abnormalities of Integumentary Structures	244
10 Connective Tissues and Skeletal System	
Histogenesis of Fibrous Connective Tissues and Cartilage	248
Histogenesis of Bone	253
<i>Intramembranous Bone Formation</i>	253
<i>Endochondral Bone Formation</i>	257
<i>Formation of Compact Bone from Primary Cancellous Bone</i>	259
Development of the Skeleton	260
<i>Development of Flat Bones</i>	261
<i>Development of Long Bones</i>	261
<i>Development of Joints</i>	264
<i>Formation of Vertebrae and Ribs</i>	268
<i>Appendicular Skeleton</i>	274
<i>Development of the Skull</i>	277
<i>Progress of Ossification in Skeleton as a Whole</i>	286
<i>Abnormalities of Skeletal Development</i>	290
11 The Muscular System	
Histogenesis of Muscle	292
<i>Smooth Muscle</i>	292
<i>Cardiac Muscle</i>	293
<i>Skeletal Muscle</i>	295

Visceral Musculature	297
Skeletal Musculature	298
<i>Primary Arrangement of Myotomes in Young Embryos</i>	298
<i>Muscles of Trunk and Body-wall</i>	302
<i>Muscles of Appendages</i>	304
<i>Muscles of Perineal Region</i>	306
<i>Muscles of Head and Neck</i>	306
12 Development of the Nervous System	
Functional Significance of the Various Parts of the Nervous System	315
Histogenesis of Spinal Cord and Formation of Spinal Nerves	325
<i>Ependymal, Mantle, and Marginal Layers</i>	325
<i>Neuroglia</i>	327
<i>Growth and Migration of Neuroblasts and Formation of Spinal Nerves</i>	330
<i>Formation of Sheaths about Nerve Fibers</i>	335
<i>Development of the Gray and White Matter of the Cord</i>	337
Regional Differentiation of the Brain	339
<i>The Myelencephalon</i>	339
<i>The Metencephalon</i>	343
<i>The Mesencephalon</i>	347
<i>The Diencephalon</i>	350
<i>The Telencephalon</i>	352
Ventricular System of the Brain, Choroid Plexuses, and Cerebrospinal Fluid	362
Cranial Nerves	367
Autonomic Nervous System	378
Developmental Abnormalities of the Nervous System	379
13 The Sense Organs	
General Sensory Organs	389
Organs of Taste	391
Olfactory Organ	392
The Eye	396
The Ear	415
14 Development of the Face and Jaws and the Teeth	
The Jaws	427
Nasal Chambers	430
The Palate	430
The Tongue	434
Developmental Defects of the Face, Jaws, and Palate	437
The Teeth	441
Developmental Abnormalities of Teeth	457
15 Development of the Digestive and Respiratory Systems	
Digestive System	460
<i>Digestive Tube</i>	460
<i>Histogenesis of the Walls of the Digestive Tube</i>	467

Birth and the "After-birth"	167
Hormonal Regulatory Actions During Pregnancy	170
Anomalies of Fetal-Maternal Relations	173
7 Age, Growth, and Changes in External Form of Body	
Estimation of Age and Methods of Measuring Embryos	181
Growth of Body as a Whole	183
Development of External Form of Body	189
Growth of Organ Systems	198
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Teratology	219
Gigantism and Acromegaly	224
Dwarfism	224
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9 Integumentary System	
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Glands of the Skin	239
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<i>Abnormalities of Skeletal Development</i>	290
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Histogenesis of Muscle	292
<i>Smooth Muscle</i>	292
<i>Cardiac Muscle</i>	293
<i>Skeletal Muscle</i>	295

I

Introduction

DEVELOPMENT OF EMBRYOLOGY AS A SCIENCE

How we develop before we are born has always been a matter of intriguing interest. "Where did I come from?" is one of a child's first thoughtful questions. Among primitive peoples—peoples in their cultural childhood—this same interest was urgent and intense. It is difficult for us, with our accumulated heritage of biological knowledge, to realize how completely mysterious a thing birth must have been to them. It is not strange that they invested the beginning of a new life with many strange superstitions and a tangle of folklore, and hedged it about with taboos. But always, behind the mysticism, there was at work that characteristic primate instinct of curiosity—the driving urge to find out how things happen, and why. From the earliest of written records we know that even then man had learned that birth came as a sequel to sexual union. Rooted in this knowledge there grew up powerful religions centering about the processes of reproduction, and bitter wars were fought between tribes who worshiped the male personification of sex and those who worshiped the female. For offspring meant the life of the tribe, and the deities who presided over procreation and birth must be powerful gods who would tolerate no pretenders.

There were many centuries when groping curiosity turned only toward speculation and mysticism. Aristotle's work on embryos is now of significance not because of the information he secured, surprisingly accurate as some of it was. His work is for us rather a symbol of the beginning of the turning of man's mind away from superstition and conjecture, toward observation. Unfortunately, such an approach did not take firm root. Through much of the Middle Ages the spark that the better of the Greek and Roman scholars had been attempting to fan was smothered by bigotry and authoritarianism. The comparatively few illustrations which were not copies from classical works were crudely symbolic, like the fifteenth-century drawings purporting to show the possible positions of the fetus in the uterus herein reproduced as Fig. 1, A. But the manner of approach was not the only reason for the lag in the growth of our knowledge of embryology. The early phases of development involve exceedingly minute structures, and curiosity and the willingness to learn by observation were not enough. Galen, it is true, had learned much about the structure of relatively advanced fetuses, and after the long stagnant period of the so-called "Dark Ages" Fabricius of Aquapendente (1533–1619)

I

Introduction

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produced a significant treatise, "De Formatu Foetu," which has recently been made available by Professor Adelman in a beautiful facsimile copy, bound with a careful English translation and a most interesting account of the life and times of Fabricius. But it was not until toward the close of the

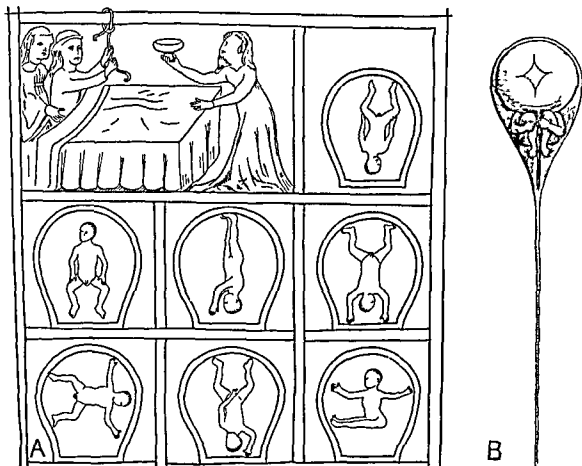


FIG 1 A, Fifteenth century illustration purporting to show fetal positions within uterus (From a manuscript in the Bodleian Library, after Sudhoff) As in many old anatomical drawings, the illustration is embellished with more or less symbolic extraneous material, in this case the woman in labor being attended by a midwife. Note that there is little accuracy or realism in the representation of either uterus or fetus. Contrast this with the beautiful drawing by Rymsdyk in William Hunter's classic treatise on the gravid uterus (see Fig 2)

B, Reproduction of Hartsoeker's drawing of a spermatozoon showing a preformed individual (Homunculus) in the head (From "Essay de Dioptrique," Paris, 1694)

seventeenth century when the microscope began to be developed into an efficient instrument that the early stages of embryology could be effectively studied

The human sperm was first seen by Hamm and Leeuwenhoek in 1677, shortly after ovarian follicles were described by de Graaf (1672). Even then the significance of the gametes in development was not understood. Two camps grew up, one contending that the sperm contained the new individual in miniature (Fig 1, B) which was merely nourished in the ovum, the other arguing that the ovum contained a minute body which was in some way

stimulated to growth by the seminal fluid. The war between the homuncualists and the ovists was almost as bitter, though not so bloody, as the ancient wars of the male and female cults of sex worshipers. Their ardor for their cause was not dampened even by the absurdity of the inevitable implication of the encasement concept—the implication that each miniature must in turn inclose the miniature of the next generation and so on for as many generations as the race was to survive.

This bootless controversy continued into the next century, finally to be laid to rest by the studies of Spallanzani (1729–1799) and Wolff (1733–1794). The work of Spallanzani is of special interest to us in that it was an initial step in bringing the experimental method to bear on embryological problems. By an ingeniously planned series of experiments, he demonstrated that both the female and the male sex products were necessary for the initiation of development.

Working contemporaneously with Spallanzani, Kaspar Friedrich Wolff, in a brilliant thesis written when he was but twenty-six years of age, set forth his conception of epigenesis. This idea of development by progressive growth and differentiation rapidly replaced the old encasement theories. Although this was an important step forward, it rested too largely on theoretical grounds to give a lasting impetus to the subject. There followed nearly a century with but little advance in our knowledge of the early stages of development, although accurate observation and recording was becoming less and less uncommon. Eloquent testimony of this trend is offered by the beautiful drawings in William Hunter's treatise on the gravid uterus (Fig. 2).

Von Baer's important work (1829) gave us the foundations of our knowledge of the germ layers in embryos. But the real significance of these layers, and of the sex elements from which they arose, could not be grasped until the cellular basis of animal structure became known. With the formulation of the cell theory by Schleiden and Schwann (1839), the foundations of modern embryology and histology were simultaneously laid. The knowledge that the adult body was composed entirely of cells and cell products paved the way for a realization of the basic fact of embryology, that the body of the new individual is developed from a single cell, the cell formed by the union in fertilization of a germ cell contributed by the male parent with a germ cell contributed by the female parent. Thus, although curiosity had been at work since before the times of written history, and with Aristotle critical observation had begun to replace conjecture, it was not until the development of the microscope, the advent of the experimental method, and the discovery of the cellular structure of the body that embryology began to become a science.

Naturally, the early workers in the field dealt almost entirely with animal material other than human, and only as the way was thus prepared could human embryology advance. The first great work which stands as the foundation of our modern knowledge of human development was "The Anatomy of Human Embryos," by Wilhelm His, published in 1880. This ushered in a period of intensive study of the minute structure of the embryonic body at

various stages of development which was given fresh impetus by the perfecting of the new technics of making serial sections (His) and the wax-plate method of making accurate scale reconstructions from such sections (His and Born)



FIG. 2 Term fetus in utero (From William Hunter "The Anatomy of the Human Gravid Uterus," 1774)

Pre-eminent during this period were such workers in Europe as Keibel, Hochstetter, and Kollmann, and Minot and Mall in America

During the latter part of the nineteenth century and the first part of the twentieth, the framework of our knowledge of embryonic structure was well

built. Many details still remain to be filled in as our technical methods improve, but the major morphological changes which occur during development are now reasonably well known. Building on this foundation, present workers in the field are directing their efforts largely toward the experimental analysis of the underlying factors which initiate and regulate development. Dramatic as have been some of the recent advances in the early localization of developmental potentialities, in the attempts to isolate organizing substances, and in the field of hormonal control of the reproductive cycle, we still stand only on the threshold of this newer phase of embryology.

EMBRYOLOGY AS A SUBJECT IN THE MEDICAL CURRICULUM

The youth of embryology as compared with such subjects as gross anatomy has made it comparatively a newcomer among the basic sciences of the medical curriculum. Now, when centuries of study have given us an ever more complete mastery of gross morphology, interest is turning increasingly toward the study of the more subtle underlying growth mechanisms by which this adult structure is established. The medical student rarely fails to appreciate the essential necessity of a thorough knowledge of gross anatomy, but in the harrassed transitional period of his first year in medical school a student may not take time to think out just why he is required to study embryology. This is not surprising, for the applications of embryology are, for the most part, less direct than are those of gross anatomy. Its service lies rather in the rational interpretation of other subjects that it alone makes possible.

Not until he becomes enmeshed in a maze of anatomical details does the student begin to realize his need of some knowledge of how adult conditions became as they are, to lead him beyond anatomical memorizing to a comprehension of anatomy. Having no familiarity with the structural and functional abnormalities encountered in clinical practice, he can scarcely be expected to realize how many of these conditions can be interpreted only from a knowledge of embryological phenomena. Knowing pathology, neurology, and obstetrics only by name or by a catalog prospectus, he can not be expected to see in advance how much his embryological background will help him in these subjects. Familiar with only the most superficial manifestations of the manner in which injuries to the various tissues of the body are repaired, he does not sense intuitively that the mechanism of tissue repair is essentially the mechanism by which that particular tissue was originally formed in the embryo. It is, therefore, only fair to the student confronted by a heavy curriculum to point out to him that embryology is more than just an interesting field of knowledge—that in reality it is a subject which will be of constantly increasing value to him as he goes on with his training and practice.

In planning a text-book of embryology for medical students, one of the troublesome problems presenting itself involves the question of the preliminary training the student may be expected to possess. It is of the utmost

importance that new work should start on firm ground. On the other hand, nothing but boredom and wasted effort result from undue repetition. In view of the present prerequisites for admission to medical school, it seems reasonable to assume that one taking up the study of human embryology will not be without a considerable background of biological information, although the exact extent of this background necessarily will vary greatly among individual students. For the great majority, certainly, it would seem unnecessary to include any preliminary review of such essentials as protoplasmic activity, cell structure, cell division, the aggregation and specialization of cells to form the fundamental tissues, and the basic principles of evolution and heredity. In the pressure of a crowded medical curriculum it is not feasible to repeat such work for the benefit of the minority who lack it. Likewise in writing this book, intended primarily for medical students, it has not seemed justifiable to increase its bulk by the inclusion of any considerable amount of material in the field of general embryology which for most students would be repetitious. The few students, therefore, who start their study of human development without a broad biological foundation will find it desirable, in connection with the early part of their course in embryology, to do collateral reading in some of the more elementary books which are readily available.

NECESSITY OF LABORATORY STUDY

An adequate course in embryology necessarily must be based on the laboratory study of actual material. No amount of didactic instruction, however effectively it may be presented, can take the place of work done by the student himself. In the laboratory, with critical and encouraging guidance, students can be led to become active acquirers instead of passive recipients of information.

The problem of laboratory material for a course designed to give medical students a knowledge of human embryology is not a simple one. Human embryos in the vitally important stages during which the various organ systems are being established can not be procured in sufficient numbers for class use. Fortunately, during these early stages, the development of all the mammals is fundamentally the same. The specific characteristics of any form emerge but slowly, and relatively late. It is, therefore, quite possible by using young embryos of other species to give students the opportunity of studying at first hand the same processes which go on in the early development of the human body.

The stages of mammalian development which commonly receive most attention in the laboratory are those in which the body form is well defined and the various organ systems are just appearing. For the beginner these stages constitute the most critical part of the subject. If the student successfully follows the emergence of the various organ systems from undifferentiated primordial tissues to a point where he can recognize the beginnings of familiar adult structures, his troubles are largely past. The chief difficulty in embry-

ology lies in getting a start among strange names and unfamiliar structural conditions. It is in recognition of this fact that so large a proportion of the laboratory work in most courses is spent on relatively young embryos. Nothing but first-hand work on their unfamiliar topography will fix it in the student's mind and give him a clear understanding of the origin and interrelations of the organs there taking shape.

To facilitate the correlation of laboratory work on nonhuman embryos with a text presenting the story of human development, a number of illustrations based on pig embryos have been included along with illustrations showing corresponding stages in human development. It is hoped that this procedure will bring vividly to the student the fact that he is not as greatly handicapped by not having human material for study as he might at first think. The developmental processes involved are what we are striving to understand, and they are much the same in all the higher vertebrates. Our situation might be compared to that of a person trying to learn about automobile engines. He would not be seriously handicapped if there were one particular type of car he could not lay hands on to pull to pieces, provided he could do what he liked with half a dozen other makes all built on the same general plans.

The fact that a variety of different species of embryos may be used in the laboratory to illustrate embryological processes must not be allowed to divert one's attention from the major sequence of events. For the specialist, detailed differences in the way the chick and the pig and the human embryo form such structures as their mesonephric tubules may be of considerable interest. But the beginning student must focus his attention on the process of mesonephric tubule formation without allowing himself to be unduly perturbed by detailed species differences. If his efforts are directed toward grasping the logical thread of the story of development, and if each step in its unfolding is mastered before the next step is attempted, the work should be easy and interesting. The growth of an embryo involves a progressively constructive series of events. A knowledge of preceding stages and an appreciation of the trend of the developmental processes by which conditions in one stage are transmuted to different conditions in the next stage are direct and necessary factors in acquiring a real comprehension of the subject. Just as historical events are led up to by preparatory occurrences and are followed by results which in turn affect later events, so events in development are presaged by preliminary changes and, when consummated, in their turn affect later steps in the process.

Reproductive Organs; Gametogenesis

REPRODUCTIVE ORGANS

Any logical account of prenatal development must start with a consideration of the phenomena which initiate that development. It is necessary to know more than the mere structure of the conjugating sex cells. We must know something of how they are produced and of the extraordinary provisions

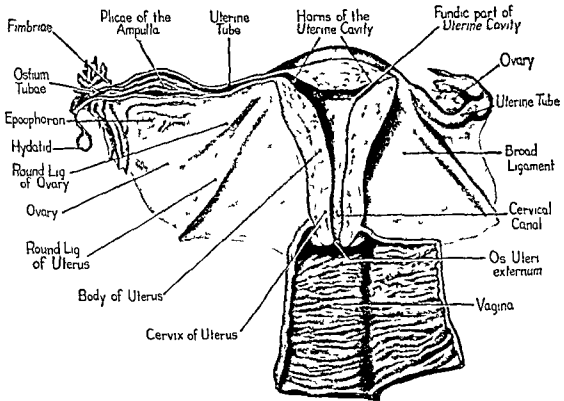


FIG 3 Internal reproductive organs of the female, spread out and viewed in ventral aspect (Modified from Rauber-Kopsch *Lehrb u Atlas der Anat des Menschen*) Vagina, uterus, and right uterine tube have been opened to show their internal configuration

which insure their union in such a place and at such a time that each is capable of discharging its function. Of vital importance, also, are the changes in the body of the mother that provide for the nutrition of the embryo during its intra-uterine existence, and for its feeding during the relatively long period after birth when it can not subsist on food such as that eaten by its parents. Before it is possible to deal with any of these things intelligibly, it is

necessary to become familiar with the main structural features of the reproductive organs

Female Reproductive Organs The reproductive organs in the female and their relations to other structures in the body are shown in Figs 3 and 4. The paired gonads—the *ovaries*—are located in the pelvic portion of the abdominal cavity. Each ovary lies in close proximity to a funnel-like opening at the end of the corresponding uterine tube. About this abdominal orifice of the tube, in the human female, are characteristic fringelike processes of highly vascular tissue which are known as *fimbriae*. When an ovum is liberated from the surface of the ovary, it enters the fimbriated end of the uterine

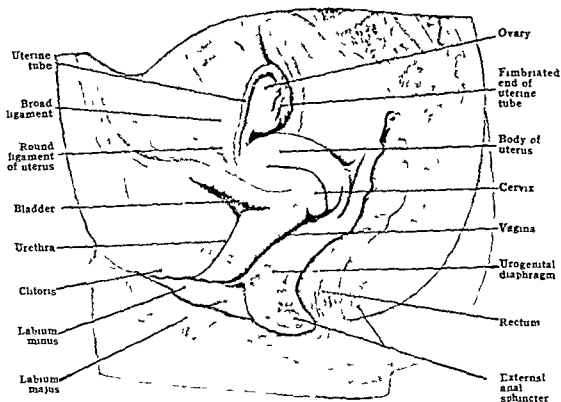


FIG 4 Sagittal section, adult female pelvis (Slightly modified from Sobotta "Atlas of Human Anatomy," courtesy, G. E. Stechert & Co.)

tube and passes slowly along the tube to the uterus. There, if it has been fertilized, it becomes attached and nourished during prenatal development.

The human *uterus* is a pear-shaped organ which in the nonpregnant condition has thick walls, richly vascular and well supplied with smooth muscle. The body of the uterus is continuous caudally with the neck or *cervix*, a region characterized by an attenuated lumen, thick walls, and glands of a different type from those occurring in the body of the uterus. The *cervix* of the uterus projects into the upper part of the *vagina*, which serves the double function of an organ of copulation and a birth canal.

Male Reproductive Organs The general arrangement and relationships of the male reproductive system are shown in Fig 5. The *testes* do not lie in the abdominal cavity as is the case with the ovaries, but are suspended in a pouchlike sac called the *scrotum*. The sex cells produced in the testes must

pass over an exceedingly long and elaborate series of ducts before reaching the outside. From the convoluted or *seminiferous tubules* where the spermatozoa (spermia)¹ are formed, they find their way through short straight ducts—the *tubuli recti*—into an irregular network of slender anastomosing ducts known as the *rete testis*. From the rete testis the spermia are collected by the *ductuli efferentes* which in turn pass them on by way of the much coiled duct of the *epididymis*, into the *ductus deferens*. At the distal end of the ductus deferens is a glandular dilation known as the *seminal vesicle*. As the name implies, it has been believed that the seminal vesicles served as sort of reservoirs in which the spermatozoa were stored pending their ejaculation. Recently the conviction

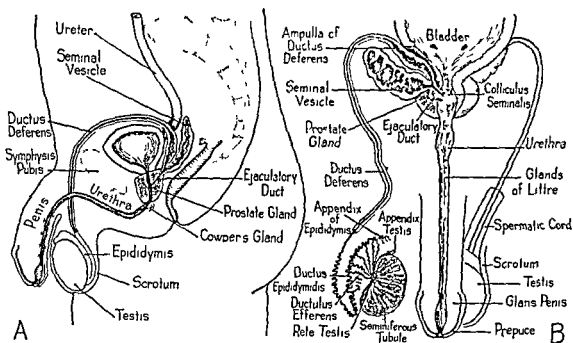


FIG. 5 Diagrams showing arrangement of male organs of reproduction (Slightly modified from Dickinson "Sex Anatomy," courtesy, The Williams & Wilkins Co.) A, Schematized lateral view projected on body outline B, Plan of sex organs spread out in frontal view

has been gaining ground that the spermatozoa are stored in the epididymis and ductus deferens, and that the seminal vesicles are primarily glandular organs which produce a secretion serving as a vehicle for the spermatozoa and possibly contributing to their nutrition.

When, during coitus, the spermatozoa are discharged, they enter the urethra by way of the ejaculatory ducts (Fig. 5). At the same time, the contents of the seminal vesicles, the prostate gland, and the bulbo-urethral glands (Cowper's glands) are forcibly evacuated into the urethra, providing a fluid medium in which the spermatozoa become actively motile. Thus

¹ There are many instances in embryology where two or more synonymous words are in common usage. To facilitate collateral reading some of the most frequently encountered synonyms have been inserted parenthetically.

mixture of secretions with spermatozoa suspended in it (semen)² is swept out along the urethra by rhythmic muscular contractions

GAMETOGENESIS

The manner in which the sex cells are produced in the gonads demands attention less cursory than that accorded the sex organs as a whole. There are moreover, many fundamental biological concepts in connection with the production of gametes which profitably can be re-emphasized in their relation to embryology.

Continuity of Germ Plasm The germ cells (sex cells or reproductive cells), which are the spermatozoa of the male and the ova of the female, are collectively known as gametes. In the process of fertilization, a male and a female gamete unite to form a single cell, the zygote, from which a new individual develops. Germ plasma is the term applied to that line of cells which, by successive divisions, give rise to the gametes. The cells which take no direct part in the production of gametes and which cease to exist with the death of the individual are called somatic cells. Thus among the myriads of cells that make up the individual and the organs that maintain his vegetative existence (brain, liver, heart, kidneys, bone, etc.) there are a limited number of germ cells that function in the perpetuation of the race—an unbroken line that has existed since the beginnings of life on earth. The conjugating gametes alone pass on the entire hereditary dowry of the species, not only from the immediate parents but also from all their ancestors.

It is readily apparent, therefore, that each person is a mosaic of his past. Looking ahead instead of backward, it is equally apparent that the entire future of any species depends on the germ plasma held in trust within the bodies of the individuals now living. For this reason the germ plasma is of paramount interest to all thinking persons. Whatever changes for good or ill the germ plasma undergoes will inevitably be written into the history of the race. Fortunately, very early in the life of an individual, the germ plasma is segregated in the gonads and not subject to most of the diseases from which the somatic cells suffer. But the germ plasma, even though not directly affected, may nevertheless suffer indirectly through a poor environment forced on it by an unhealthy body.

Of greater importance still is the nature of the combination of germ plasma which occurs in each generation when the two gametes fuse in fertilization. As surely as either gamete brings into the new combination defective germ plasma, so surely will both the body and the germ plasma of the new individual suffer therefrom.

Heredity and Environment Volumes have been written as to whether heredity or environment has the greater influence on the individual. The most bitter and most verbose phases of these controversies have centered on man's

² In addition to being used as a convenient means of giving synonyms parentheses have been used to introduce technical terms which may be unfamiliar. In such cases the term, as has been done here, is placed in parentheses following a characterizing phrase.

behavioral and intellectual life, where home and school environment play such obviously important rôles. Unfortunately, in this field, judgments have been based too little on sound biological observations and too much on "wishful thinking." It is so comforting to believe that if only we could find the right sociological and educational formulas, we could make what we would out of any kind of hereditary material. Such issues are beclouded by the fact that the laws of heredity are intricate and still further by the genetically mixed character of human beings, for *Homo sapiens* is not always sapient with regard to his own breeding.

Since all of us are "mosaics" in inheritance, low-grade offspring may occasionally confront intellectual and successful families with the defects of a forgotten ancestor, and highly successful sons and daughters may appear in the homes of the ignorant and indigent as reminders of a brighter past. Yet in spite of these conspicuous and much overemphasized sporadic cases, biological laws are inexorable and, by and large, "like begets like." That child must be considered most fortunate who has "selected his ancestors" with the greatest number of good traits to take after.

To recognize the fact that heredity is of outstanding importance does not belittle the significance of environment. Heredity provides the materials on which environment operates, but environment determines how well these materials are conserved and utilized. A crude analogy may be drawn from our everyday experience with instruments or machines. What is built into them in their manufacture corresponds to what we receive by heredity, the manner in which they are subsequently used corresponds to environment. No amount of intelligent use and careful maintenance can make a mechanism fabricated of poor materials into a long-enduring and highly efficient instrument of precision. However, abuse of a potentially fine mechanism may make it function far less satisfactorily than a similar mechanism made of poorer materials but used with intelligence and conserved with care. Environment creates nothing. Its importance lies in the way in which it determines how fully we realize, or how tragically we fall short of, our hereditary potentialities.

Such things as parental care and education are regarded by the biologist as falling in the general category of external environmental factors. There are more subtle environmental factors within the body itself, surrounding and influencing the various essential organs. In the development of the individual some of these internal environmental factors are of extraordinary importance. For example, the lens of the eye is formed from the ectoderm of the head where it is stimulated by the optic cup as it grows out from the underlying brain. If the young optic cup is transplanted so that it lies beneath the ectoderm of the back, this area of ectoderm which normally has nothing to do with eye formation will grow a lens. If the optic cup is transplanted somewhat later it will be found to have lost its power to induce lens formation in its new location. So it is apparent that there is not only the interaction of one growing part on another, but also an important factor of timing. If the specific effect is not exerted at the critical time it ceases to be effective.

In so far as the internal environment of the various parts of the developing body depends on the presence of the proper materials in the proper places at the proper times, it is largely determined by heredity. But the internal environment may be damagingly affected by external environmental factors such as malnutrition or disease. A potentially ideal heredity and internal environment both go for naught if the embryo's mother contracts such a severe pneumonia that an abortion results.

The germ cells, which are at once the bearers of hereditary traits and the raw material on which internal and external environment work, are carried in the gonads. Each germ cell has its inheritance, which gives it the potentiality of developing almost exactly as its lineal ancestors did before it—*almost exactly*, for in some yet unknown way some germ cells do change, as evidenced by the fact that species now and again show the sudden changes which the geneticists call mutations. Many attempts have been made to modify the germ plasm experimentally and to produce by artificially induced mutations new individuals different in some particular from their ancestors. Alcohol, lead, and other poisons have been tried on the supposition that they might damage the germ plasm and so cause production of inferior offspring. Ironically enough, in some cases, superior strains of rats or guinea pigs resulted from such experiments, but this outcome probably was attributable to raising the average by killing off the inferior individuals. A similar effect has long been produced in domestic animals by selective breeding and the ruthless killing off of the less desirable stock.

It was only recently that real mutations were artificially induced by massive doses of x-rays. The mutants thus produced "breed true"—i.e., the offspring exhibit the peculiarities induced in their parents when the parents were still in the gamete stage. Such cases may be classed in a broad sense as "inheritance of acquired characters," and constitute the only ones that may be considered proved. Heretofore no mutilative treatment of adult individuals even for many generations (as, for example, circumcision) has in the slightest affected the race genetically.

A curious piece of folklore may be mentioned here because physicians still encounter it among their uneducated patients, namely, the belief that a former mating may in some manner influence the offspring of a subsequent mating. The fancied resemblance to a previous husband said to be exhibited by the offspring of a second husband was "explained" on this basis. Needless to say, telegony, as this fantastic belief is called, lacks every vestige of scientific support.

Early History of Primordial Sex Cells In an adult the spermia in the testis and the eggs in the ovary are easy to recognize. A study of these definitive gametes alone does not, however, give any clue as to their origin in the development of the individual. When did it first become possible to recognize the germ plasm as such? Can the cellular ancestors of the sex cells be traced to very early stages or does the germ plasm, when we attempt to follow it back, soon lose its identity, becoming indistinguishable from somatic cells? These

early phases of the history of the gametes, at the present time, are far from being thoroughly worked out

For all vertebrates, including man, there have been described in very young embryos certain large cells in the yolk-sac that stand out in contrast with their neighbors. This happens long before it is possible to tell whether an embryo is to become male or female—indeed, before any gonad is laid down. These large cells have been identified by some investigators as primordial sex cells and they believe that they migrate from the yolk-sac ento-

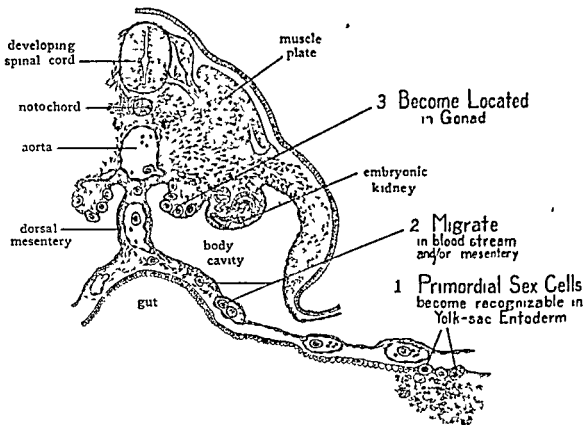


FIG 6 Schematic section through mid body region of a young embryo, illustrating manner in which the primordial germ cells are believed by some investigators to originate in yolk-sac entoderm and migrate thence to developing gonad

derm to their final location in the gonad. This interpretation is illustrated schematically in Fig 6. In various mammalian embryos, including the human, such primordial sex cells have been described in the primitive gut, in the mesoderm surrounding it, and finally in the epithelium of the developing gonad. The definitive germ cells, male or female, are believed by some investigators to arise, by successive mitotic divisions, from these primordial germ cells. There are other investigators, however, who deny that these large cells seen in the entoderm are really germ cells. Still others grant that they may be germ cells of a primitive line but contend that these particular cells die and are resorbed, and that the definitive germ cells come from new generations of cells that arise later from the germinal epithelium of the gonad. Whether or not they are direct descendants of these much discussed large cells of yolk-

sac origin, primordial germ cells very early become unmistakably recognizable in the germinal epithelium of the embryonic gonad, and groups of them grow from the germinal epithelium into the deeper living tissues of the gonads (Fig 359)

In the gonads of both sexes the earliest cells to grow in become organized into cords. In the male they become the seminiferous tubules and eventually give rise to the sex cells. In the female these primordial strands of cells persist in the medulla of the ovary in vestigial form as the so-called medullary cords, but do not give rise to sex cells. Their occasional pathological hypertrophy is supposed to be responsible for the appearance of male secondary characters in women. The definitive ova are derived from cells which arise in subsequent waves of proliferation from the germinal epithelium. This proliferation occurs most conspicuously before birth, and since the times of Waldeyer (1870) it has been commonly believed that a girl is born with all the ova she will ever have. According to this view these ova are supposed to lie dormant until sexual maturity, when they are stimulated, in groups, to undergo their final development. Of each group that starts to develop, some undergo degeneration, but on the average one egg cell a month is supposed to be brought to maturity and liberated by ovulation. Some eggs that eventually mature, according to this still widely credited view, would have lain dormant in the ovary for from 45 to 50 years.

Evidence recently has been adduced, however, which tends to show that unfertilized ova are in reality short-lived cells (Allen, 1922, Evans and Swezy, 1931). These authors believe that the ova seen in the ovaries of infants and sexually immature girls all degenerate and that they are replaced by new proliferations from the germinative epithelium. On the same interpretation, the partially differentiated eggs in the ovary of a sexually mature adult today are practically all doomed to die during the succeeding month, and will be replaced by new proliferations from the germinal epithelium. This process is described as a cyclical one and as continuing throughout the sexually active life of the individual. According to this view, the human female develops, not merely the quarter- to half-million potential ova which the newborn infant possesses, but many more during her reproductive life from menarche to menopause. The overproduction of potential gametes in the female would thus more nearly approach that existing in the male, although in the female relatively few of them are actually brought to maturity. Which of these conflicting views ultimately proves to be correct is of far more than theoretical embryological significance. If the newer view as to the continuous production of ova is correct, the surgical handling of ovarian lesions should be more conservative than is now usually the case, since even a small piece of ovarian germinal epithelium might produce functional ova.

Early Differentiation of Testes Shortly after the primordial sex cells become established in the gonads, sexual differentiation begins. It is then necessary to trace the course of events separately for the two sexes (Fig 7). During the embryonic life of the young male individual the primordial sex

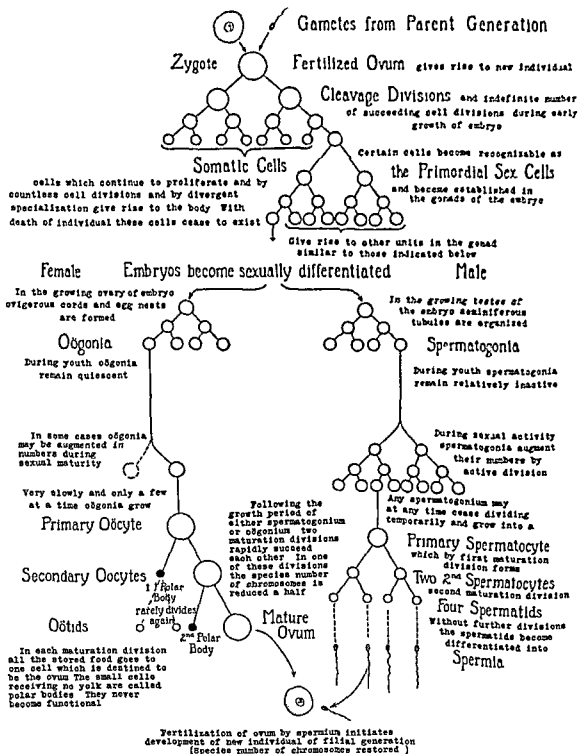


FIG 7 Chart outlining, for one generation, the history of the gametes and the germ plasm from which they are derived

cells grow from the epithelial covering of the testis into its substance and there become organized to form the seminiferous tubules. Many cell generations are of course occupied with the fabrication of a seminiferous tubule, but the cells which eventually constitute its wall can, nevertheless, be traced back to the primordial sex cells of the germinal epithelium of the gonad. When they become established in the walls of a seminiferous tubule, the cells are known as "sperm mother cells" or *spermatogonia*. At this stage of development the spermatogonia constitute the individual's "germ plasm." During early post-natal life and the growth period, these future gamete producers remain relatively quiescent and undeveloped. Their inactivity stands in sharp contrast to the rapid proliferation and differentiation of the remainder of the cells which go to make up the body of the growing individual. It is as if the spermatogonia, thus set apart, were hoarding their energy for the next generation. Only when the individual becomes sexually mature do they begin intensive activity.

Spermatogenesis The mature testes contain a large number of much convoluted seminiferous tubules. Their position and relations are schematically indicated in Fig. 5. This illustration, however, gives no conception of the astonishing total length of the gamete-producing tubules crowded within the testes. It has been estimated by Osterrud and Bascom from a study of serial sections that the total length of the seminiferous tubules from one testis of a mature boar pulled out straight and placed end to end would reach 3200 meters. When one realizes the total length of these tubules, it is not difficult to understand how each ejaculate of semen contains millions upon millions of fully formed, active spermatozoa.

In man and the relatively few other animals that have no special breeding periods, spermatogenesis goes on continuously during sexual maturity. The maturation divisions and the subsequent metamorphosis of the spermatids are believed to occupy about 10 days. The different tubules of an active testis exhibit all phases of the process, but since the tubules seem to be swept by waves of activity, a given area of a particular tubule is likely to show a strong preponderance of some particular stage.

If we examine the spermatogonia lying at the periphery of an active adult seminiferous tubule, we see many mitotic figures (Fig. 8, 2). A cell arising from such a spermatogonial division may do one of two things: (1) It may cease dividing for a time and, by growing to a size markedly larger than its parent, become differentiated as a *primary spermatocyte* (Fig. 8, 3), or (2) it may remain like its parent and continue to produce other spermatogonia. The new cells thus formed take the place of the spermatogonia which have grown into spermatocytes and moved out of the spermatogonial layer toward the lumen of the tubule. Thus, some of the cells always remain in the peripheral part of the tubule as spermatogonia and furnish a constant source of new cells ready for conversion into spermatocytes.

Once a cell goes through the growth phase which differentiates it so that we call it a primary spermatocyte, its future history is very definitely deter-

mined. It first undergoes a mitotic division resulting in the formation of two smaller daughter cells called *secondary spermatocytes* (Fig 8, 5). Each of these secondary spermatocytes, without any resting period which might allow the cells to grow to the size attained by their parents, promptly divides again and forms two *spermatids* (Fig 8, 6, 7). Cell division then ceases and each

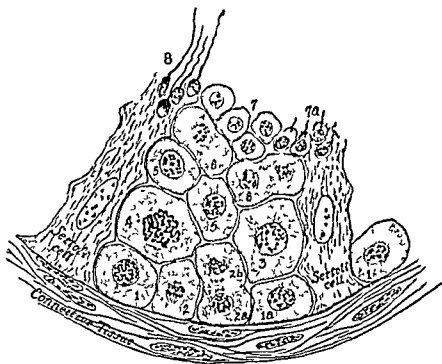


FIG 8 Semischematic figure showing small segment of the wall of an active seminiferous tubule. Sequence of events in production of spermia is indicated by the numbers. A spermatogonium (1) goes into mitosis (2), producing two daughter cells (2a, 2b). One daughter cell (2a) may remain peripherally located as a new spermatogonium, eventually coming to occupy such a position as 1a. The other daughter cell (2b) may grow into a primary spermatocyte (3), being crowded meanwhile nearer the lumen of the tubule. When fully grown the primary spermatocyte will go into mitosis again (4), and produce two secondary spermatocytes (5, 5). Each secondary spermatocyte at once divides again (6, 6), producing spermatids (7). The spermatids become embedded in the tip of a Sertoli cell (7a), there undergoing their metamorphosis and becoming spermia (8) which, when mature, are detached into the lumen of the seminiferous tubule.

spermatid is gradually transformed into a fully formed, potentially functional male gamete, a *spermatozoon*, or spermium.

In the metamorphosis of a spermatid the nuclear material becomes exceedingly compact to form the bulk of the head of the spermium, the centrosomal apparatus of the spermatid undergoes an elaborate modification to give rise to the motile axial filament of the tail of the spermium, and the cytoplasm is reduced greatly in bulk, giving rise to an envelope with a tiny thickened cap (acrosome) about the head of the spermium, and a delicate investment of the axial filament of its middle piece and tail (Fig 9). During

their transformation, the spermatids are embedded in the cytoplasm of nurse or supporting cells (*Sertoli cells*) which lie at intervals in the wall of the seminiferous tubule (Fig 8, 7a, 8) It is believed that in some way the Sertoli cells transfer to the metamorphosing spermatids food materials they themselves obtain from the small blood vessels in the connective tissue investing the

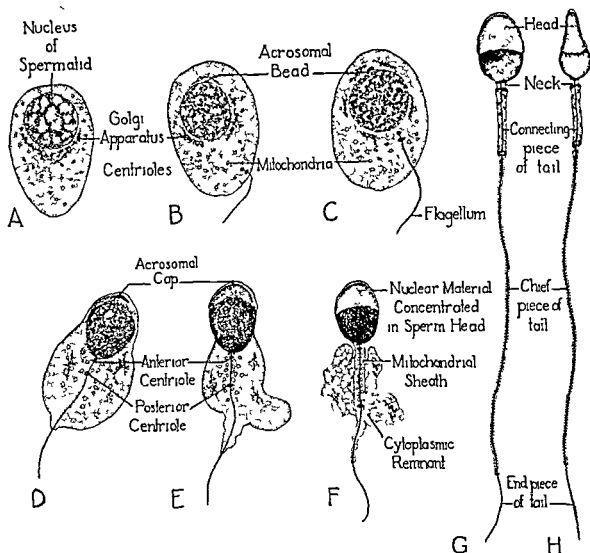


FIG 9 Stages in maturation of spermatids (Modified from figures by Gatenby and Beams Quart J Micr Sci, Vol 78, 1935)

seminiferous tubule When they are fully mature, the spermia free themselves from the Sertoli cells and are carried out along the lumen of the seminiferous tubule toward the epididymis

In the microscopical study of semen, abnormal spermatozoa of a variety of types are not infrequently seen (Fig 10) It seems probable that such spermia in the race to meet and penetrate an ovum, are outstripped by the millions of normal spermia with which they are surrounded, and that, taking no part in fertilization, they can not be concerned with the production of abnormal embryos So little, however, is known with any degree of certainty, either as to the significance of these abnormal spermia or as to the causes of abnormal development, that any such statement must be made tentatively and not dogmatically

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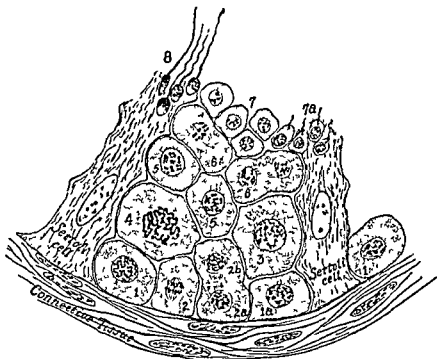


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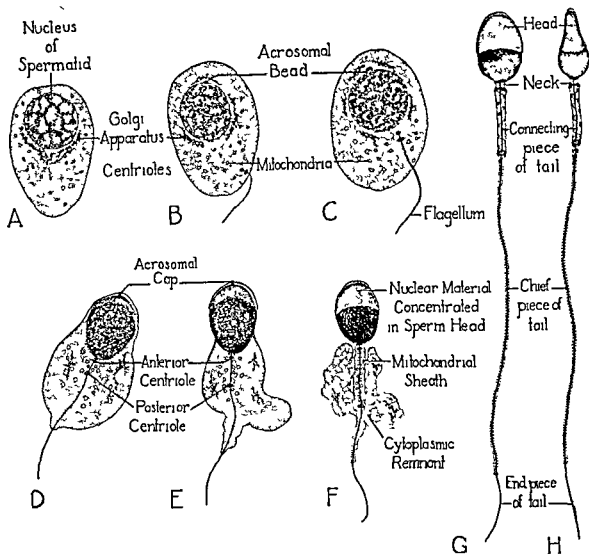


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Early Differentiation of Ovary The origin, migration, and early segregation of the primordial sex cells in the gonad take place, as we have seen, before there is any sexual differentiation observable in the embryo. Consequently, in tracing these phenomena, we established a common starting

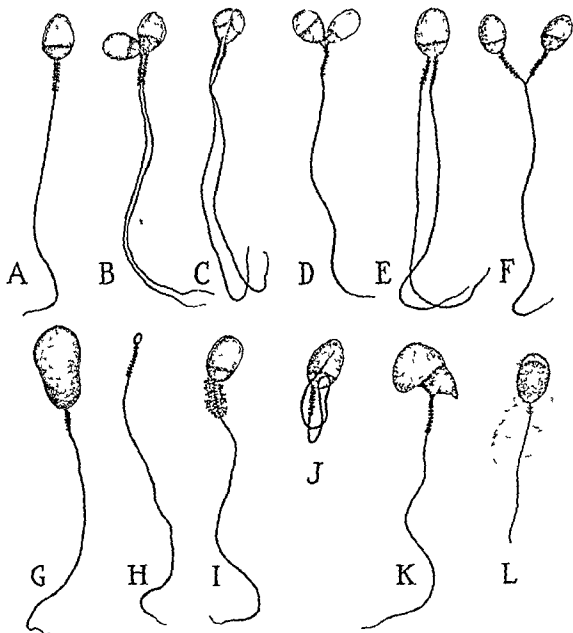


FIG. 10 Various types of abnormal human spermatozoa. Normal spermatozoon for comparison is shown in A, $\times 1600$ (A, I, after Maximow, B, C, D, E, G, K, after Broman, F, H, J, L, after Moench and Holt)

point for following later developments in the female as well as in the male (Fig. 7). Even when the indifferent stage is passed and it is possible to say definitely that a given embryo is developing into a female, conditions in the ovary are at first similar in a general way to conditions in the testis at a corresponding stage of development. The sex cells which have appeared in the epithelium investing the growing ovary push centripetally into the ovarian

connective tissue in a manner very suggestive of the way *seminiferous tubules* arise in the testis. The cords of sex cells thus invading the ovarian stroma are known as "egg tubes" (*ovigerous cords*, Pflüger's tubes)

From this point on, the structural resemblances of the growing gonads in the two sexes become less and less apparent. A striking homology, however, exists throughout the entire series of changes in the germ cells themselves, and should not be lost sight of even though the later phases occur in organs differentiating as divergently as the ovary and the testis. In both spermatogenesis and oogenesis we can recognize a succession of three comparable phases: (1) A period of proliferation in which spermatogonia and oogonia, by a series of repeated divisions, augment the available numbers of potential germ cells, (2) a period of cell growth to *primary spermatocyte* or *primary oocyte* signaling the end of proliferation and the approach of maturation, and finally (3) the period of maturation which involves always two, and only two, cell divisions characterized by the special nuclear processes of chromosome reduction.

Oogenesis Although the phases of the processes are directly comparable, the details of spermatogenesis and oogenesis show many interesting contrasts. Their differences are correlated with the antithetical nature of the specializations in the gametes themselves. In the male, small, actively motile gametes with no stored food material are produced in enormous numbers. The energy which, in the male, goes into quantity production, in the female is expressed by more elaborate preparation of the gametes and the storing of food material in their cytoplasm. The ova thus become very large, nonmotile cells and compared with spermatozoa, relatively few of them are brought to maturity.

Very early in the history of the *oögonia* the tendency to concentrate effort on a few cells, rather than spread it over many, becomes apparent. In the *ovigerous cords*, and in the egg nests which are formed by the breaking up of the cords, one or two of the cells will almost always be found to have grown larger than their neighbors (Fig. 11). All the cells of the cords or nests are potentially oogonia. Those which show enlargement are already beginning their growth to form *primary oocytes*. The cells which lie adjacent to one of these growing oogonia, figuratively speaking, forego their own chances of becoming oocytes and arrange themselves as a protecting and food-purveying investment about the future ovum. The entire group of cells thus formed is known as a *primary ovarian (Graafian)³ follicle* (Figs. 11, 12). The cells surrounding the oocyte proliferate rapidly and form an increasingly thick covering about it. With continued growth there appears in the layer of follicle cells a fluid-filled

³ Formerly it was customary to name structures after the man first describing them. For example the ovarian follicle in all the older literature will be found designated as the Graafian follicle, after the Dutch anatomist Reynier de Graaf (1641-1673). While this old custom is interesting in that it preserves for us the names of pioneer workers, the present tendency is to make our nomenclature more logical and more easily remembered by replacing proper name designations with names descriptive of the structure. Such a change can be accomplished only gradually, however, and in many cases as is true in the present instance a proper name has become so firmly established through long usage that it is necessary to know it as a synonymous term in order not to be confused by its constant appearance in reference reading.

cavity which expands very rapidly (Fig 12, D-G) This cavity is called the *antrum*, and the fluid which fills it is known as the *liquor folliculi*

During the earlier phases of its development the follicle has usually pushed its way deep into the connective-tissue framework (stroma) of the ovary When the follicle begins to fill with fluid it starts to work gradually toward the surface As its size is still further increased it comes to protrude from the ovary, appearing in the living subject, when exposed by operation, much like a water blister Such a follicle is nearly ready to rupture and release the contained egg cell

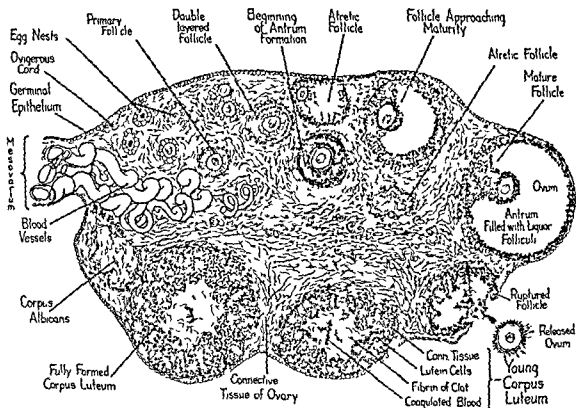


FIG 11 Schematic diagram of ovary showing sequence of events in origin, growth, and rupture of ovarian (Graafian) follicle, and formation and retrogression of corpus luteum Follow clockwise around ovary, starting at mesovarium

At this stage the follicle and the egg cell have acquired a degree of differentiation which demand closer scrutiny The egg cell contained in the nearly ripe follicle is commonly called the *ovum*, but if we used the terminology which emphasizes the homologies of development in male and female gametes, we should call it by its more cumbersome name, *primary oocyte* It has grown to a size many times that of the follicle cells which surround it, and its abundant cytoplasm is dotted with granules of stored food material (yolk, deutoplasm) Since the total yolk content in mammalian ova is relatively small and uniformly distributed, the nucleus is not crowded to one side but is centrally located within the cytoplasm (Fig 12) The cell membrane has become considerably thickened In many of the older texts it still keeps its old name of "*vitelline membrane*," which, along with such obsolescent

terms as "germal vesicle" for the nucleus and "germal spot" for the nucleolus, was given it before the true significance of "the egg" as a specialized cell was understood

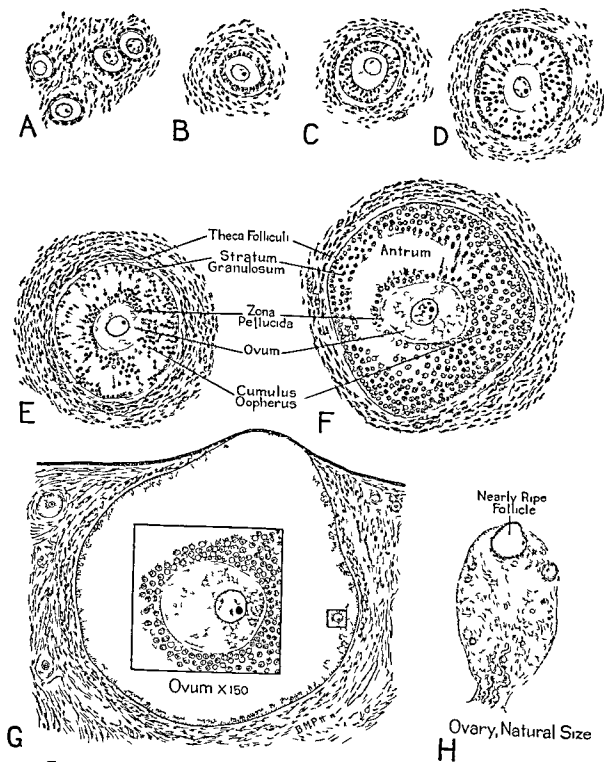


FIG 12 Drawings showing a series of stages in development of the human ovum and ovarian follicle A-F, projection drawings $\times 150$ In G the follicle is $\times 15$ but the inset detail of the ovum is $\times 150$ like the other drawings in the series

Surrounding the ovum is a transparent, noncellular, secreted layer known as the *zona pellucida* (Fig 12) ⁴ Outside the zona pellucida is an investment of

⁴ In some forms this zone exhibits delicate radial striations When these are conspicuous the term

radially elongated follicle cells constituting the so-called *corona radiata*. Some of these radially arranged cells usually continue to cling to the ovum for a time after it is discharged (Fig 14, A)

Turning our attention to the follicle, we find that as it has matured it has acquired an increasing amount of fluid within the antrum. In this process most of the follicle cells are crowded peripherally to constitute the so-called *stratum granulosum*, or cellular layer, of the follicular wall. Outside the *stratum granulosum*, the immediately surrounding ovarian connective tissue has become condensed about the growing follicle. This secondary connective-tissue investment is known as the *theca folliculi* (Fig 12). It may be differentiated into an outer, densely fibrous layer, and an inner layer, less conspicuously fibrous, which contains many cells and numerous small vessels, but there is no sharp boundary between these layers, and the *theca* itself blends gradually into the surrounding ovarian stroma.

At the point where the ovum lies among the follicle cells they form a hillock projecting from the *stratum granulosum* into the antrum. This hillock is known as the *cumulus oophorus*. When first formed it is broad and low. As the follicle approaches maturity the *cumulus* becomes more elevated and somewhat undercut (Fig 11). Finally, the ovum is carried on a slender stalk of cells which readily releases it and allows it to escape in the follicular fluid set free when the follicle ruptures.

Ovulation. The precise mechanism which precipitates the rupture of the ovarian follicle is not as yet known with certainty. In all probability there are several factors involved. We know from the way mature follicles protrude at the ovarian surface that the fluid pressure within them is considerable. As the follicle bulges under this pressure its connective-tissue envelope (*theca folliculi*) is squeezed against the connective-tissue capsule (*tunica albuginea*) of the ovary. It seems not unlikely that this process compresses the small blood vessels where the bulging is most pronounced, thus reducing the nutrition of the region affected and eventually lowering the resistance of the tissues. Such a mechanical effect of fluid pressure might well pave the way for the rupture of the follicle. Underlying the development of the follicle and the accumulation of its contained fluid, there is certainly the stimulus of a hormone produced in the anterior lobe of the pituitary. According to the recent work of Joseph Smith, there appears to be a marked increase in the concentration of salts in the liquor folliculi as the time of rupture approaches. The endosmotic effect of such a concentration may well be a precipitating factor in bringing the internal fluid pressure to a point where rupture of the follicle occurs.

However future work may evaluate the importance of the several possible causative factors involved, we know that the rupture of the follicle when it does occur is an abrupt, almost explosive, process. Hill, Allen, and Kramer have succeeded in making a detailed micromoving-picture record of ovula-

zona radiata instead of *zona pellucida* is applied to this same layer. The term, although descriptively appropriate, is unfortunate because it is so frequently confused with the totally different cellular investment outside of it called the *corona radiata*.

tion in the rabbit, and their film shows with great vividness the rapid terminal bulging of the follicle culminating in sudden rupture with a gush of follicular fluid which brings with it the ovum surrounded by its radiate corona of follicle cells (Figs 13, 14). A slight hemorrhage can be seen to accompany the rupture of the follicle.

When an ovum is thus liberated from the surface of the ovary, it momentarily enters the abdominal cavity. Sometimes it fails to be picked up promptly in the funnel-like opening in the uterine tube. In such a case it is possible for spermia to work their way from the tube into the peritoneal cavity and there fertilize the ovum. The ovum will then begin to develop and attach itself to the viscera, thus bringing about an abdominal pregnancy. Fortunately, such an eventuality is relatively uncommon, for it calls for prompt surgical intervention, and its early recognition may severely test the physician's diagnostic ability.

The danger of an ovum thus failing to find its way into the uterine tube is not so great as one might suppose from the loose relations of the uterine tube to the ovary. The ovum is liberated in close proximity to the tubal orifice into a region of the abdominal cavity which is more or less circumscribed by the adjacent gut, the broad ligament, and the pelvic wall. At the time of ovulation the smooth muscle of the uterine tube is known to be highly active and the fringelike processes of its open end are believed to sweep about, close against the ovary. This action, together with the current created by the ciliated epithelial lining of the tube, tends to capture the ovum and start it on its way toward the uterus. That this mechanism is extraordinarily effective is indicated by certain rare cases on record in which, following the surgical removal of an ovary on one side and a tube on the other, ova from the remaining ovary were picked up by the intact tube on the opposite side.

Atresia of Follicles. By no means do all the follicles that start to enlarge go on to ovulation. Ordinarily, a woman will bring to maturity but a single ovarian follicle each four weeks. Examination of the ovary shortly before ovulation is due to occur, however, will reveal the presence of several follicles well advanced in their development. Toward the close of their growth period something seems to happen to all but one of these follicles which abruptly causes them to cease development and begin to undergo regressive changes. The degeneration of follicles which have thus apparently started to mature is called atresia (Fig 15). Atresia of follicles is by no means limited to animals which ordinarily produce but a single offspring at a time. Among animals in which multiple births are the rule, follicles are also formed in excess and reduced by atresia to a number consonant with the number of young the particular species in question ordinarily bears in a litter. Occasionally in women atresia does not reduce the number of follicles to the usual single one, and, if a fruitful coitus occurs at such a time, multiple offspring will result.

Corpus Luteum. The history of an ovarian follicle is by no means closed when it has liberated its contained ovum. There remain in the ovary the great bulk of the follicle cells and the connective-tissue theca which surrounded the

radially elongated follicle cells constituting the so-called *corona radiata*. Some of these radially arranged cells usually continue to cling to the ovum for a time after it is discharged (Fig 14, A)

Turning our attention to the follicle, we find that as it has matured it has acquired an increasing amount of fluid within the antrum. In this process most of the follicle cells are crowded peripherally to constitute the so-called *stratum granulosum*, or cellular layer, of the follicular wall. Outside the *stratum granulosum*, the immediately surrounding ovarian connective tissue has become condensed about the growing follicle. This secondary connective-tissue investment is known as the *theca folliculi* (Fig 12). It may be differentiated into an outer, densely fibrous layer, and an inner layer, less conspicuously fibrous, which contains many cells and numerous small vessels, but there is no sharp boundary between these layers, and the theca itself blends gradually into the surrounding ovarian stroma.

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follicle before its rupture. These structures become involved in the development of the corpus luteum. The corpus luteum, so called because of the yellow color it exhibits in fresh material, grows very rapidly in bulk for a time, and becomes an organ of internal secretion—that is to say, it produces a secretion which is not discharged by way of ducts, as is the case with ordinary glandular secretions, but which is liberated into the blood stream. The secretion diffused from a ductless gland into blood vessels, and carried by the blood stream to

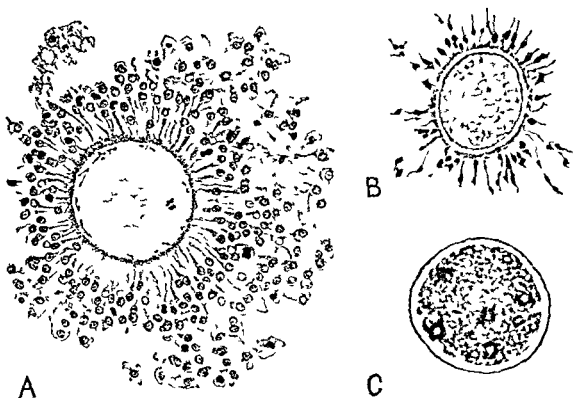


FIG. 14 Three photomicrographs ($\times 200$) of the primate ovum

A, Human oocyte from a follicle 14 mm in diameter, which was about ready to rupture (After Stieve) Note the chromosomes of the first maturation division and the radially arranged follicle cells constituting the so-called "corona radiata"

B, Similar stage of the ovum of a Macaque monkey (After Corner) Note the spindle of the first maturation division

C, Human ovum washed out of the uterine tube. Photographed before fixation (Carnegie Coll., 6289, courtesy W. H. Lewis) Note the thickened zona pellucida and the loss of the cells which constituted the corona radiata. The small, highly refractive areas in the cytoplasm are due to lipid droplets

some other place in the body where it exerts a definite physiologic effect, is called a hormone. The probable action of the particular hormone produced by the corpus luteum in preparing the lining of the uterus to receive and implant the fertilized ovum is a subject to which we shall have occasion to return later in connection with the sexual cycle. For the moment we are concerned with the origin and structure of the corpus luteum itself.

When the ovarian follicle ruptures, escape of most of the contained fluid and contraction of the stroma of the ovary reduce the size of its lumen. Bleeding of the small vessels injured in the rupture of the follicle may partially fill the collapsed antrum with blood which, together with the residue

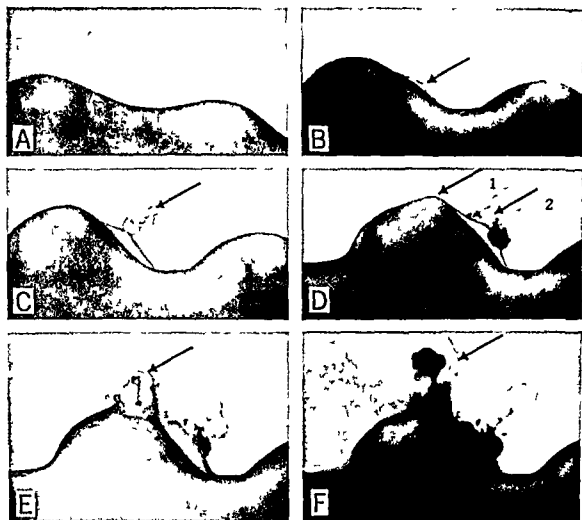


FIG 13 Enlargements of single frames of a time-lapse motion picture showing ovulation in the rabbit (From Hill, Allen, and Kramer, *Anat Rec*, Vol 63, 1935)

A, Profile view of two follicles about $1\frac{1}{2}$ hours before rupture

B, Same follicles about $1\frac{1}{2}$ hour before rupture

C, Exudation of clear fluid in early phases of rupture

D, At arrow 1, a new follicle becomes conical as the time of its rupture approaches. At arrow 2, the exudate from the follicle shown starting to rupture in C has become more abundant and has some blood (dark) incorporated in its mass

E, The follicle indicated by arrow 1 in D is now beginning to rupture. The blood-tinged exudate from the follicle which started to rupture in C and showed more vigorous exudation in D (arrow No 2) can be seen partly behind the more recently rupturing follicle

F, The rupture of the follicle which is indicated by the arrow in E. Time elapsed between the photographs shown in E and F, 8 seconds. The ovum is carried out with this final gush of fluid from the ruptured follicle

of the follicular contents, promptly becomes consolidated as a clot. A recently ruptured follicle thus filled with blood-tinged coagulated material is called a corpus hemorrhagicum. Recent work seems to indicate that, in addition to



A Corpus Luteum of Ovulation



B Corpus Luteum of Pregnancy

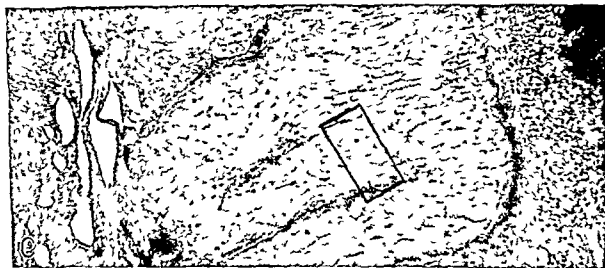
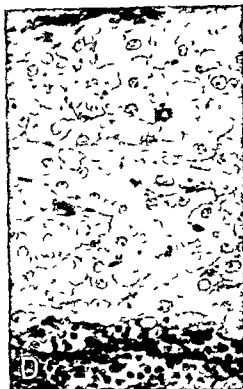


FIG. 16 Structure of corpora lutea. A, Sketch, actual size, of ovary with corpus luteum of ovulation. B, Sketch, actual size, of ovary with corpus luteum of pregnancy. C, Photomicrograph ($\times 60$) of segment of corpus luteum from capsule through to central clot-filled lumen. D, Photomicrograph ($\times 225$) of a small area of luteal tissue taken from the area marked in C. B, C, and D from case operated on for tubal pregnancy, embryo 17.9 mm (7 weeks fertilization age).

the small amount of blood coming from the bleeding incidental to follicular rupture, there is a secondary hemorrhage of the small vessels in the corpus luteum at the time of the following menstrual period.

The coagulum at the center of the newly formed corpus luteum is soon attacked peripherally by phagocytic white blood corpuscles and becomes

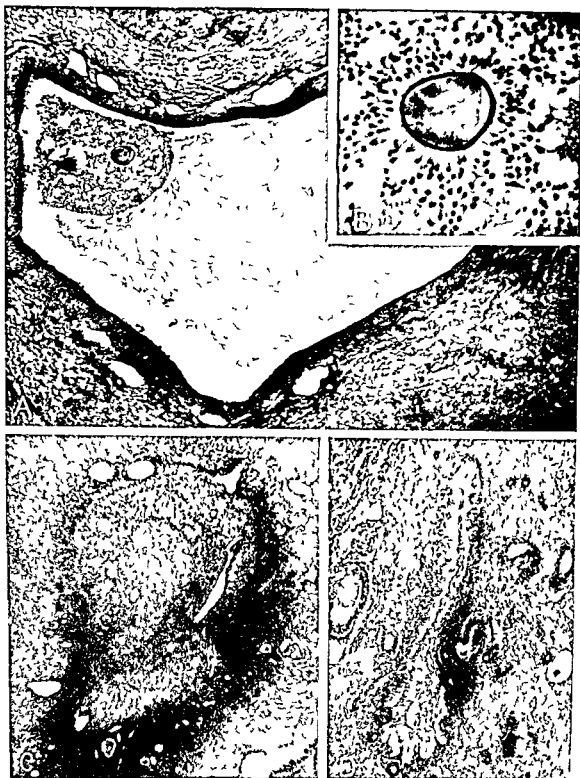


FIG 15 Photomicrographs showing three stages in follicular atresia. A, Early regressive changes in follicle ($\times 75$) B, Ovum and cumulus cells ($\times 200$) (C), Antrum shrunken and filled with young fibroblasts ($\times 50$) D, Scar similar to corpus albicans following a corpus luteum, but smaller ($\times 50$)

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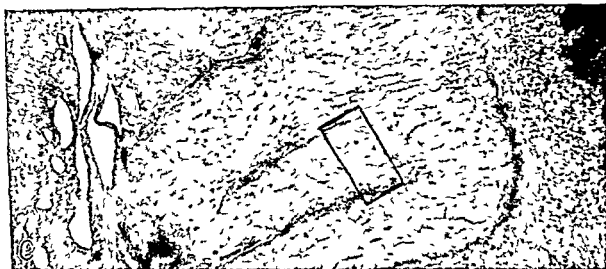


FIG 16 Structure of corpora lutea A, Sketch, actual size, of ovary with corpus luteum of ovulation B, Sketch, actual size, of ovary with corpus luteum of pregnancy C, Photomicrograph ($\times 60$) of segment of corpus luteum from capsule through to central clot-filled lumen D, Photomicrograph ($\times 225$) of a small area of luteal tissue taken from the area marked in C B, C, and D from case operated on for tubal pregnancy, embryo 17.9 mm (7 weeks fertilization age)

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The coagulum at the center of the newly formed corpus luteum is soon attacked peripherally by phagocytic white blood corpuscles and becomes

progressively reduced in extent. Concomitantly, the follicular cells of the stratum granulosum increase greatly in both number and size, and crowd into the area formerly occupied by the clot. At the same time, small vessels from the connective-tissue theca penetrate the enlarged mass of follicle cells

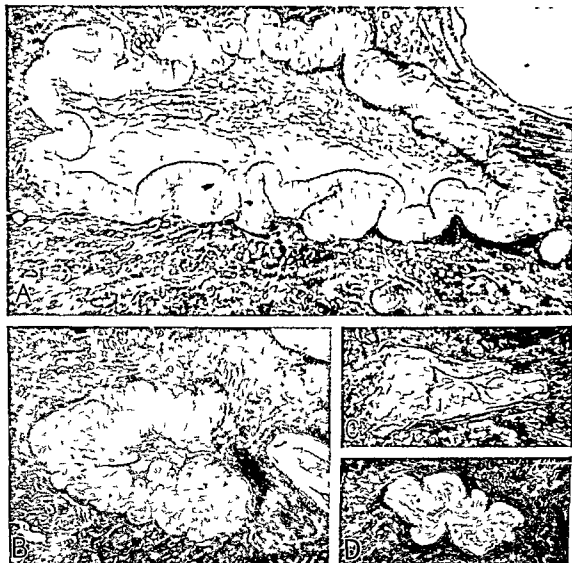


FIG 17 Corpora albicantia of different ages ($\times 225$)

A, Shortly after regression of luteal cells. Note extensive central area partially filled with coagulum.

B, After central area has been nearly obliterated and corpus albicans has become more compact.

C, Further stage in same process of shrinkage.

D, Final stage which persists for a long time marking the site of an ovarian follicle and the corpus luteum which followed it.

and ramify among them. These vessels bring in with them numerous small cells of thecal origin which become packed in among the more conspicuous cells which originated from the stratum granulosum (Fig 16). Thus, both layers of the follicular wall contribute to the corpus luteum although the most conspicuous and characteristic cellular elements are derived from the follicle cells of the stratum granulosum.

Corpora lutea normally develop from all ruptured follicles, but if the liberated ova are not fertilized, the corpora lutea soon degenerate. If, however, the ova are fertilized and implanted in the uterus, the corpora lutea undergo a greatly prolonged period of growth and persist much longer before degenerating. This difference in the history of the corpora lutea is recognized by designating the short-lived ones as the *corpora lutea of ovulation* and the ones which persist longer as the *corpora lutea of pregnancy*. Histologically, they exhibit the same structural picture, their differences being apparently quantitative rather than qualitative.

When either type of corpus luteum begins to degenerate, the retrogressive changes are in the nature of a fibrous involution—that is, the cellular part of the organ disintegrates and fibrous connective tissue takes its place. As this connective tissue grows older and more compact, it gradually takes on the characteristic whitish appearance of scar tissue. Finally, all that is left in the ovary to mark the site of what was first ovarian follicle, and subsequently corpus luteum, is a shrunken patch of scar tissue called a *corpus albicans* (Figs 11–17).

Formation of Polar Bodies The maturation of the “ovum” (primary oocyte) begins at just about the time of its liberation from the follicle. As in the male, two divisions occur in rapid succession, but instead of four functional gametes being formed as an end-result there is in the female only one. At each maturation division, two cells are formed. But one of these cells receives practically all the stored food material of the primary oocyte, while the other receives little or none and soon degenerates. The cell receiving no yolk material was called a “polar body” before its significance was understood. It is, of course, an oocyte with a reduced share of cytoplasm.

The gross results of the two maturation divisions in the female are schematically summarized in Figs 7 and 18. The first maturation division ordinarily occurs in the ovary just before the rupture of the ovarian follicle. In this division the primary oocyte divides to form two secondary oocytes. One of these receives little cytoplasm and is called the first polar body. The second maturation division does not occur until the ovum has been released from the ovary, and, in mammals, is unlikely to be completed unless the ovum has been penetrated by a spermatozoon. In the second maturation division the secondary oocyte which has pre-empted all the stored food material divides again, and in this division also the bulk of the cytoplasm goes to one of the two resulting ootids, which is then commonly called the “matured ovum.” The other ootid is the second polar body. Occasionally the first polar body undergoes a second division, clearly indicating the homology of the maturation divisions in the two sexes (Fig 7). Usually, however, it degenerates before such a division occurs. The second polar body likewise degenerates soon after it is formed, leaving, of the four potential ootids, only one which becomes functional.

Chromosomal Reduction in Maturation The events in the maturation of male and female gametes which have just been discussed are but the more evident phases of the process. There are changes of profound significance

progressively reduced in extent. Concomitantly, the follicular cells of the stratum granulosum increase greatly in both number and size, and crowd into the area formerly occupied by the clot. At the same time, small vessels from the connective-tissue theca penetrate the enlarged mass of follicle cells

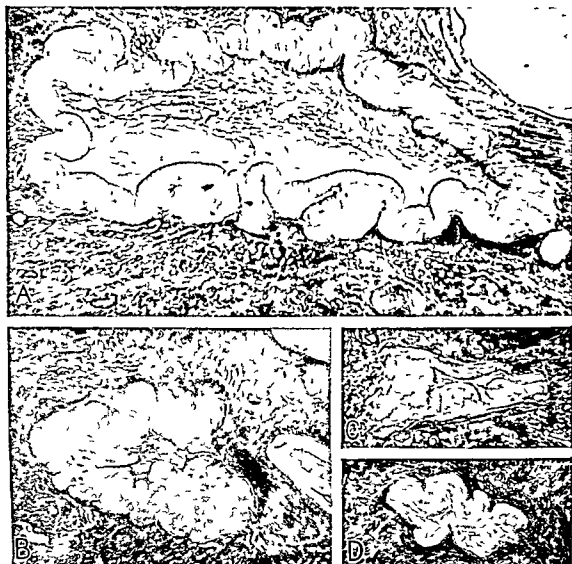


FIG. 17. Corpora albicantia of different ages ($\times 225$)

A, Shortly after regression of luteal cells. Note extensive central area partially filled with coagulum.

B, After central area has been nearly obliterated and corpus albicans has become more compact.

C, Further stage in same process of shrinkage.

D, Final stage which persists for a long time marking the site of an ovarian follicle and the corpus luteum which followed it.

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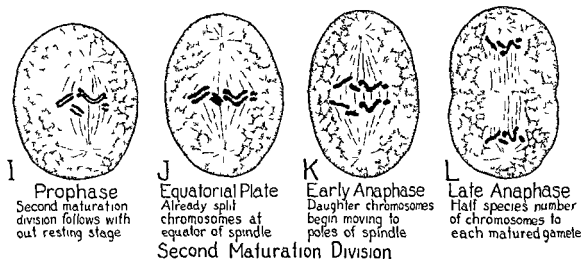
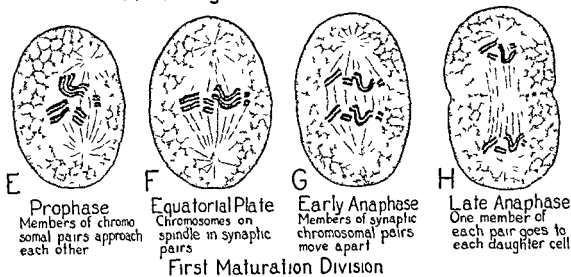
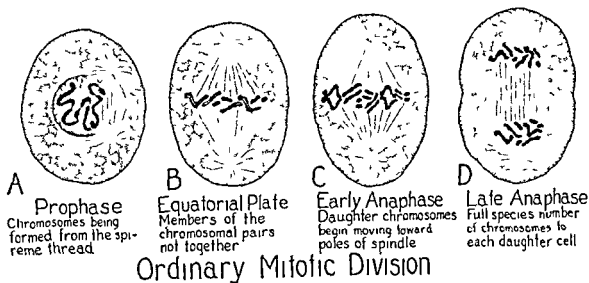


FIG 19 Diagrams showing schematically differences between chromosomal behavior in an ordinary mitotic division and in the maturation divisions. To simplify the drawing the species number of chromosomes is taken as eight, instead of the 48 characteristic of man.

going on at the same time in the nuclear material of the maturing sex cells. The essential part of the nucleus which is involved is the chromatin. In a resting cell the chromatin is dispersed through the vesicular nucleus in the form of small granules. In a dividing cell these granules coalesce into bodies of varying length and shape, the chromosomes. Because of their behavior in

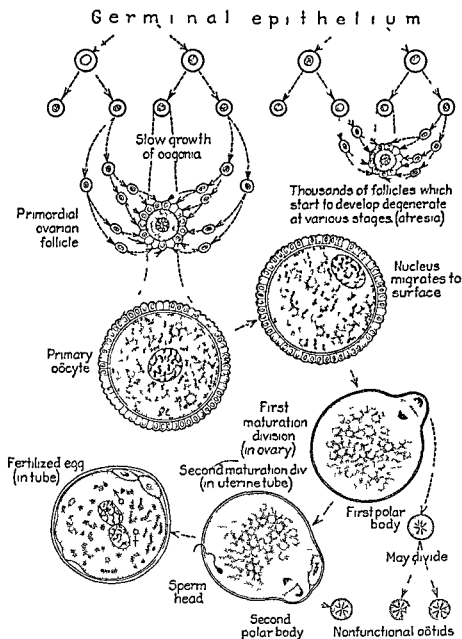


FIG 18 Diagrams illustrating multiplication, growth, maturation, and fertilization of mammalian egg

cell division, in the maturation of the germ cells, in parthenogenesis, and in relation to genetics, we know that the chromosomes play a most important part in heredity and as determiners of the course of individual development.

In the mitotic division of a cell (Fig 19, A-D) the chromosomes line up in the equatorial plane of the spindle, split lengthwise with mathematical exactness, and each daughter chromosome passes to one of the daughter cells.

sons enable the cytologist to chart the chromosomes of a cell, similar pair by similar pair (Fig 21, A) The significance of this interesting pairing of the chromosomes will be further discussed in connection with maturation and fertilization

Geneticists confirm and amplify the findings of the cytologists as to the biological importance of chromosomes The hereditary principles, or "genes," are thought of as self-perpetuating bodies in the chromosomes, each gene determining a particular "unit character" The genes for different characters are believed to be situated each in a specific location in the chromosome This is indicated by so breeding organisms that specific characters are changed Microscopical examination of the germ cells in the individuals that show or lack the particular characters which are being studied show the correlated changes in chromosomal pattern Of course genes, like atoms, are ultra-microscopic in size, and the biologist can only infer their existence and

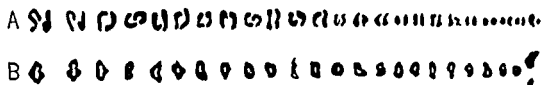


FIG 21 Human chromosomes (After Evans and Swezy, Mem Univ Cal, Vol 9, 1929)

A, the 48 chromosomes of a spermatogonium arranged into 23 fairly well matched pairs and the X-Y pair (last pair on the right)

B, The chromosomes in synapical pairs as they appear in a primary spermatocytic (reductional) division Note the unmated X and Y chromosomes at the right of the series

arrangement by observing the combination and recombination of the materials in which they are believed to be present, just as the physicist deduces the electronic structure of an atom which he can not see Thus from many and varied sources the evidence is steadily growing that the chromosomes are the all-important links in the endless chain of heredity—a definite number of pairs maintained constant in all the cells of an individual by mitosis, and carried into the bodies of the next generation by the gametes

Significance of Maturation While the maintenance of the species number of chromosomes in an individual is dependent on mitosis, it is preserved from generation to generation by the processes of maturation and fertilization By the maturation divisions, it will be recalled, we mean to designate the final two divisions of spermatogenesis or oogenesis In these divisions the number of chromosomes in the gametes is reduced to half the number characteristic of the species When, in fertilization, a male and a female gamete, each bearing half the species number of chromosomes, unite with each other, the species number of chromosomes is re-established in the individual of a new generation

Cytologists have worked out the mechanism of the maturation divisions with great care in many forms Stripped of detail, and without reference to the many peculiar modifications encountered in different animals, the reduc-

Chromosomes and cytoplasm then both grow until they are ready to divide again. Not only is it true that every cell comes from a pre-existing cell, as Virchow maintained nearly a century ago in his famous phrase "omnis cellula e cellula," but we now know that every chromosome comes from a previously existing chromosome. And we know also that the daughter cell is like the parent cell because it has a similar chromosomal content.

It is known, moreover, that in any species of animals all the body cells have the same number of chromosomes. In *Ascaris megalocephala*, the roundworm of the horse, the number is only four in addition to the sex chromosomes, by virtue of this simple condition this form has contributed much to our

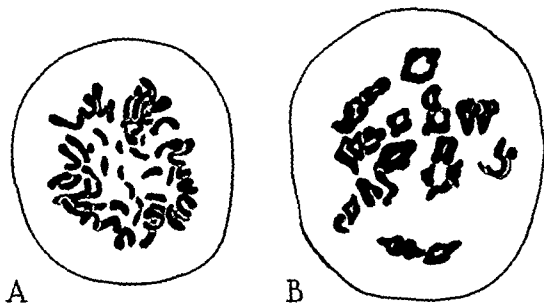


FIG. 20 The chromosomes of the germ cells of man (After Painter, J. Exp. Zool., Vol. 37, 1923). The dividing cells are represented as viewed from a pole of the spindle so that the arrangement of the chromosomes in the equatorial plate is clearly shown. A, The 48 separate chromosomes of a spermatogonial division ($\times 4000$). B, Prophase of primary spermatocyte division showing the chromosomes in synaptonemal pairs ($\times 4000$).

knowledge of chromosomes. *Drosophila*, the fruit fly, has but eight chromosomes, and, since these flies are easily reared by thousands, they have contributed extraordinarily to our knowledge of the mode of inheritance. The opossum has 22, a simple condition for a mammal, which helped Painter in his discovery of the sex chromosomes of mammals. In following the lead of this earlier work, Painter was able to identify the sex chromosomes of man and to establish the human species number of chromosomes as 48.

If the chromosomes present in the cells of any species are carefully studied, it becomes apparent that each chromosome has its own characteristics. They are not all alike, as is unfortunately suggested by many oversimplified diagrams of mitosis. Furthermore, the chromosomes are present in pairs, the members of which are similar in size and shape. The members of a pair are not usually located next to one another on the spindle of an ordinary somatic mitosis (Figs. 19, B, 20, A), but methodical micromerements and compar-

Consideration of the chromosomal behavior during reduction will make it apparent that the cells formed by the reduction division must contain different hereditary potentialities because they contain different chromosomes, not halves of the same chromosomes as in an ordinary mitosis. With man's 48 chromosomes it has been estimated that some 17 million different combinations are possible at the time of the reduction division. Nor does this cover all the possibilities, for during synapsis there may be interchange of genes, a process the geneticist calls "crossing over," which still further multiplies the possible genetic combinations. What hereditary possibilities are discarded into the polar bodies and thrown off from the female gamete and what retained in the mature ovum, is a matter of chance distribution. What potentialities find their way into the particular sperm which alone out of millions of its fellows fertilizes the ovum, is likewise fortuitous. "In this way there is produced sufficient stability to insure continuity and at the same time sufficient variety to insure progress. For the offspring will in the main resemble progenitors which have successfully lived in the prevailing conditions of the past, but will exhibit sufficient variability among themselves to insure that some of them shall successfully live in any conditions likely to arise in the future" (William Patten, in "Life, Heredity, and Evolution")

tion to half the species number of chromosomes is accomplished by a cell division in which the chromosomes are not split in the metaphase in the manner of a somatic mitosis, but instead are redistributed. In this process of redistribution half of them go bodily to one daughter cell and half to the other (Fig 19, E-L)

In maturation the separating of the chromosomal pairs is preceded by a special preparatory process termed *synapsis* which occurs in the prophase of a maturation division but not in an ordinary mitosis. If, under ideal conditions, we look at the spindle of an ordinary cell in mitosis (Fig 19, B), we can recognize the members of the chromosomal pairs by their size and shape, but the members of the pairs appear to lie scattered in haphazard fashion. When, during the prophase, distinct chromosomes took shape these chromosomes aggregated at once and without any evident scheme of arrangement at the equator of the spindle. In contrast, during the prolonged prophase of a maturation division, the members of the chromosomal pairs come to lie close to each other and so remain for some time. This pairing off of the chromosomes is called *synapsis*.

The pairs of chromosomes, still in intimate association, then gradually move to the equator of the spindle (Fig 19, E, F). In most forms which have been carefully studied, including man, these synaptic pairs of chromosomes as the first maturation division is approached have a peculiar quadripartite appearance which has led to their designation as a "tetrad." This condition is due merely to the fact that, as occurs in an ordinary mitosis, the splitting of the chromosomes themselves is already apparent before the actual migration of the daughter chromosomes toward the poles of the spindle begins. Thus a tetrad is nothing but a synaptic pair of chromosomes in which each member of the pair is already showing the sort of internal division which occurs at the corresponding stage in any mitosis (Cf Fig 19, B, F).

The characteristic thing about the process of reduction is that instead of each chromosome completing its splitting and moving toward the pole of the spindle, as is the case in an ordinary mitosis, the two members of the synaptic pairs are separated from each other, one going bodily to each pole of the spindle (Fig 19, F-H). This means that following such a division each daughter cell receives one member of each of the chromosomal pairs that are present in the somatic cells of the species, or half the species number. Cytologists call this half complement of chromosomes the haploid number, in contrast to the diploid, or full species, number. Usually, this reduction of the chromosomes takes place in the first of the two maturation divisions (Fig 19, E-H). In the second maturation division, which follows the first without the return of the chromosomes to the usual resting stage, the chromosomes of each daughter cell merely complete the division which was already begun when they went into *synapsis*. Since this involves no further reduction of the chromosomes but merely a splitting such as occurs in an ordinary mitosis, such a division, in contrast to the reduction division, is called an equational division (Fig 19, I-L).

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3

Sexual Cycle and Fertilization

SEXUAL CYCLE

Beneath the restraining influences of a complex social fabric there are operating in us the same physiologic mechanisms which make the reproductive instinct one of the greatest driving forces among all living things. Many phases of the cyclic changes in the human reproductive organs can be interpreted only in the light of our more complete knowledge of the similar recurring changes in other mammals. In them the behavioral manifestations of hormone-driven urges are uninhibited, and more important still, we can experiment on them freely under properly controlled conditions.

Perhaps the reticence which has so long shrouded matters pertaining to sex has had a retarding influence on the investigation of breeding habits and all the internal changes which are correlated with them. Perhaps the problems have been particularly intricate. Certain it is, in any case, that only very recently have we begun to acquire anything like a real understanding of the underlying physiological factors. Our knowledge is still far from complete, but some of the main points in the story have been fitted together and checked by experiment, and new information is constantly being added. As is inevitable with any subject in which our knowledge is growing rapidly, there is much difference of opinion as to the significance of certain of the observed facts. It is through the discussion and evaluation of just such divergent interpretations that further progress comes. But it is neither possible nor advisable in such a brief account as this to become involved in the points of controversy. We must content ourselves with a mere outline of the facts which seem best established and realize that even some of these facts may be subjected to different interpretations.

Sexual Cycle in Mammals Sexual periodicity is, as a rule, much less strongly developed in the male than in the female. In some animals, such as those of the deer family, there is a brief period of intense sexual activity at one particular season of the year and then a long period during which there is sexual impotence and cessation of spermatogenesis. More commonly, and especially is this true among the primates, the male is sexually potent throughout adult life. A brief period of pronounced sexual activity, when it does occur in males, is known to animal breeders as the "rutting season." It always corresponds in time with the females' period of strong mating impulse which breeders call the "period of heat" and biologists speak of as the estrus

The term estrus originally referred merely to the existence of a period of strong sexual desire made evident through behavior. As more information has been acquired about the concomitant changes going on within the body, it has become evident that this is close to the time of ovulation, and that the characteristic behavior is but an external indication that all the complicated internal mechanism of reproduction is ready to become functional. If pregnancy does not occur at this time, regressive changes follow and another period of preparation must ensue before conditions are again favorable for reproduction. This repeated series of changes is known as the estrous or sexual cycle. Its phases in the absence of pregnancy are (1) A short time of complete preparedness for reproduction accompanied by sexual desire (estrus), (2) a

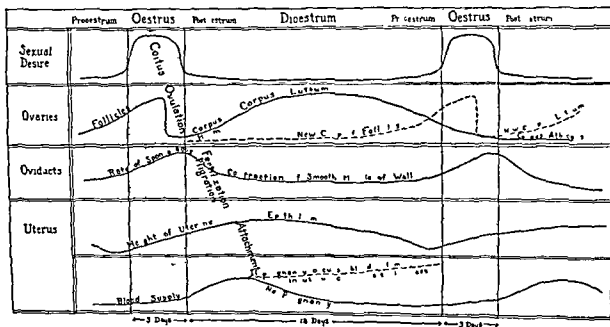


FIG 22 Graph showing correlation of changes which occur during the estrous cycle in the sow (Compiled from the work of Corner, Seckinger, and Keye) Note the coincidence of the important events leading toward pregnancy (coitus, ovulation, fertilization of the ovum and its migration through the oviduct to the uterus, and finally its attachment to the uterine mucosa) with the height of local activity as indicated by the curves

period during which the fruitless preparations for pregnancy undergo regression (post- or metestrus), (3) a period of rest (diestrus), followed by (4) a period of active preparatory changes (proestrus) leading up to the next estrus when everything is again in readiness for reproduction (Fig 22)

There is wide variation in the length of time occupied by this cycle in different animals. In some it occupies an entire year, the estrus being so placed seasonally that when in due time the young are born, conditions are favorable for their rearing. Forms having thus but one breeding season in the year are said to be monestrous. Other forms exhibit several breeding periods in a year. Such animals are said to be polyestrous. On the basis of our present knowledge it would appear that a polyestrous rhythm is the underlying condition in mammals generally. Many factors mask or modify it in different cases, but in the forms which have been most fully studied it is unmistakably

present. Accepting this proposition tentatively, it is not unreasonable to suppose that an annual estrus such as that exhibited by the deer family has become established through the suppression of other periods, primarily because of the regular recurrence of pregnancies of long duration following what was originally merely the most favorable of several estrous periods. It is well known, furthermore, that the estrous cycle may be interrupted by many things other than pregnancy. Thus starvation, extreme exposure, or severe sickness may cause the suppression of an estrus. A contributing cause in reducing a polyestrous to a monestrous rhythm, operative in the case of females failing to become pregnant, might well be the severity of the conditions under which many wild animals live during the winter, or during a dry season.

It is known with certainty that many animals, as for example the sheep, which have but one breeding season in the year when living in their wild state, develop a polyestrous rhythm when living under domestication. An underlying polyestrous condition is necessarily obscured when a pregnancy follows each estrus as occurs normally among wild animals. It becomes apparent, however, when such an animal, under conditions of domestication or under experimental conditions in the laboratory, is not permitted to become pregnant. Then following an unfruitful estrus there appears but a brief interval occupied by regression, rest, and preparation, followed shortly by another estrus. Living conditions under domestication being relatively uniform, suppression of an estrus through starvation or exposure does not occur, and the estrous periods keep recurring at fairly regular intervals until one of them is consummated by pregnancy.

Such, in barest outline, is the sequence of events in the higher mammals generally. Before considering the activating and regulating mechanisms underlying these recurring changes, it will be desirable to know in more detail the nature of the special structural alterations in the human uterus that are preparatory for receiving and embedding a fertilized ovum, and the regressive changes which occur when no pregnancy follows ovulation.

Primate Menstrual Cycle Menstruation is the term applied to the periodic discharge from the uterus of blood, mucus, and cellular debris which occurs in nonpregnant women of sexual maturity at about four-week intervals. In temperate climates menstruation usually commences at an age of 13 to 14 years and continues until the time of the menopause, which occurs ordinarily in the late forties or early fifties. The usual duration of the menstrual discharge is from four to five days, but there is considerable individual variability in the length of the period as well as in the interval at which it recurs.

Because of the insistent recurrence of menstruation, a woman is likely to use her "periods" as time landmarks in the placing of events connected with her sexual life, or with any pelvic symptoms leading to the seeking of medical advice. Perhaps this tendency has been in part responsible for the old misconception that menstruation in women corresponded with the estrous period

in lower mammals. It is now, however, well established from experimental work with many mammals that the critical event of estrus is ovulation, and in women ovulation occurs approximately midway between the menstrual periods.

The phase of the sexual cycle of lower mammals with which menstruation corresponds is that phase which occurs a short time after an unfruitful estrus and is characterized by reduction in the thickness of the mucous lining of the uterus and decrease in its blood supply (Fig. 22). One reason why this correspondence went so long unrecognized is the fact that the regressive changes in the uteri of most mammals are relatively slower than in women, and are accomplished without the sloughing of the uterine lining and the hemorrhage which give external notice of these internal events in women and in other primate females. Menstruation is not then, as formerly believed, a process signaling the preparation of a fresh, raw uterine surface in which the young embryo could readily implant itself. It is rather the "protest of a disappointed uterus," that all its elaborate preparations for embedding and nourishing a fertilized ovum have gone for naught.

Detailed consideration of the microscopical changes undergone by the lining of the uterus during the menstrual cycle is ordinarily regarded as belonging in the province of histology, and excellent accounts are available in any good histological text-book. Nevertheless, the importance of the uterine mucous membrane in the implantation of the embryo and in the formation of the placenta makes it necessary for us at this juncture to be familiar with at least the general nature of these changes. Fig. 23 reproduces photomicrographs of the mucous membrane of the uterus made to the same scale of magnification at various stages in the cycle.

Considering, first, conditions shortly after the previous period has ended (Fig. 23, A), it will be noticed that the lining epithelium has been reconstructed although it is still somewhat thin in spots. This epithelial restoration is accomplished with surprising rapidity by proliferation of the cells of the deep part of the glands, below the level involved in the sloughing process. The glands themselves in this early phase of reconstruction are relatively slender and straight, and their lumina are small and devoid of any conspicuous amount of secretion. The connective tissue supporting the glands is of a richly cellular, young-appearing type, lacking the coarse fibers usually so conspicuous in adult connective tissue. Six days after the end of the preceding period (that is to say, on the eleventh day of the cycle, which is arbitrarily regarded as commencing with the first day of flow), the mucous membrane is about 2 to 3 mm. thick (Fig. 23, B). Until the last third of the cycle is reached, no very striking changes in the general histological picture occur except the gradual increase in the thickness of the mucous membrane.

As the last third of the cycle is entered, changes in the appearance of the glands begin to become evident. The walls of the glands become irregular, the size of their lumen increases, and a conspicuous amount of secretion can be seen within the glands. There is also a striking increase in the conspicuousness

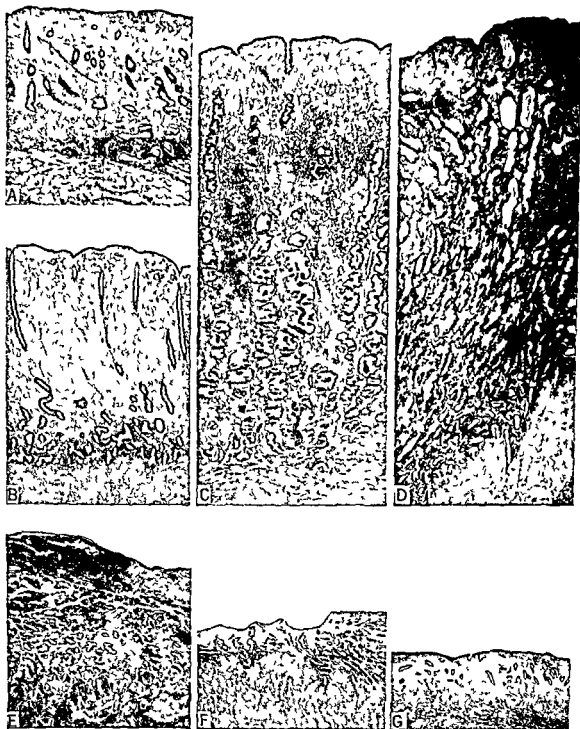


FIG 23 The histological changes in the uterine mucous membrane during the menstrual cycle (From preparations and photomicrographs loaned by Dr George W Bartelmez, reproduced $\times 20$) A, Seventh day of menstrual cycle, the endometrium is in its early growth phase B, Eleventh day of menstrual cycle, later growth phase of endometrium, time of ovulation approaching C, Twenty third day of menstrual cycle—stage of maximal secretory activity under stimulating effect of the corpus luteum D, Twenty-eighth day—menstruation imminent Note the marked edema of the superficial zone of the mucosa E, First day of menstruation F, Fourth day of menstruation G, Fifth day—transition from menstruation to early repair

of the small arteries supplying the superficial portion of the mucosa, and they extend nearer to the surface. These arteries tend to follow a spiral course and their coiling becomes much more marked at this stage. By the end of the third week of the cycle these changes begin to progress at an accelerated rate and the whole histological picture suggests heightened activity. During the week before the impending period is due to commence, these changes reach their culmination. The glands are greatly distended, the small blood vessels are engorged, and the actual thickness of the mucosa has increased from the 1 mm or less left immediately after the last period ended, to perhaps 4 or 5

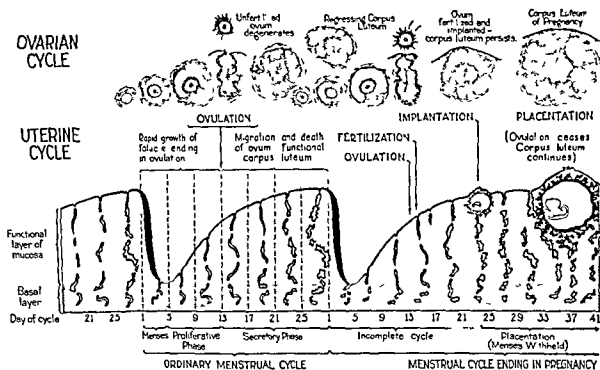


FIG 24 Graphic summary of changes in the endometrium during an ordinary menstrual cycle and a subsequent cycle in which pregnancy occurs (Modified from Schroder) The correlated changes in the ovary are suggested above in their proper relation to the same time scale

mm (Fig 23, C) This is the so-called secretory phase, when the uterus is fully prepared to implant and nourish a young embryo

If fertilization does not occur, this phase of premenstrual congestion goes over into menstruation. Immediately preceding the actual menstrual discharge is a brief phase in which there is a reduced blood flow to the superficial zone of the uterine mucosa, although the blood flow in the vessels supplying the deeper layers remains uninterrupted. In the affected superficial zone white blood corpuscles begin to migrate into the stroma and the tissues, deprived of an active circulation, begin to deteriorate. When this ischemic phase (Fig 23, D) has lasted a few hours, spiral arteries here and there start to open up and blood pours into the superficial capillaries and soon ruptures their weakened walls so that there is extravasation into the tissues beneath the epithelial lining. In a very brief time the now necrotic superficial tissue, together with the extravasated blood which remains unclotted, additional blood oozing from the freshly denuded surface, and the secretion from the

opened mouths of the glands, all start to come away together as the menstrual discharge (Fig 23, E, F) Once started, this process proceeds rapidly in a given area, but by no means is the entire uterine lining simultaneously affected During the early part of the period, area after area is involved until by the third day the uterine surface has been pretty well denuded

Repair, beginning first in the areas which were the first to be affected, is initiated promptly (Fig 23, G) According to Bartelmez, it is only a matter of a few hours before the epithelial lining is re-established over the denuded areas and the slow growth of the next intermenstrual interval commences The highly schematized diagram of Fig 24 summarizes the sequence of changes in the cycle Comparison of this figure with the actual photomicrographs of Fig 23 will make clear the significance of such things in the diagram as (1) the heavily shaded basal layer of the mucous membrane, which indicates the part not sloughed off during menstruation, (2) the differences in

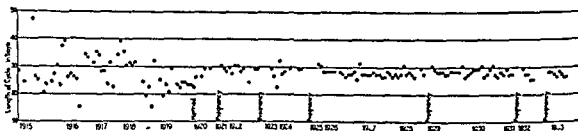


FIG 25: Chart showing lengths of menstrual cycles of a single individual for a period of nearly 20 years The days of the menses were recorded on a calendar beginning with the onset of menstruation at the age of 13 Note particularly the irregularity of the lengths of the cycles during adolescence (After Knapp, from Hartman "Time of Ovulation in Women," Courtesy, The Williams & Wilkins Co)

the shape of the glands, and (3) the startling differences in the total thickness of the mucous membrane diagrammed for different parts of the cycle

Although the length of the menstrual cycle is ordinarily stated as being 28 days, this is merely a convenient statistical average When the length of the cycle is noted month by month and recorded on a calendar, it becomes apparent that there is much more variation than is commonly recognized There are great differences in the length of cycles in different individuals and in the same individual at different times Particularly instructive are individual records kept over long periods Such records (Fig 25) show very strikingly the irregularity of the intervals between menstrual periods which is so usual in young women

Ovarian Cycle Although its rhythm is subject to even more individual variability and its vagaries are far less easily ascertained, the ovary as well as the uterus is known to undergo cyclical changes As is the case with menstruation, ovulation begins at puberty and continues at approximately four-week intervals until the menopause, except when interrupted by pregnancy and lactation, by pathological conditions, or by disturbances in the endocrine regulatory mechanism The parallel periodicity and the obvious functional association of ovulation and menstruation suggest their control by interlocking

mechanisms, but the interdependence of the two processes is not direct and absolute, for either can, under certain circumstances, occur in the absence of the other

The nature of the process of ovulation has been considered in the preceding chapter. The question which is of interest to us at the moment is the time relation between ovulation and menstruation, for although the intermenstrual and interovulation intervals are of about the same duration, we know that the critical events of the cycles do not coincide. The first trustworthy information on the time of ovulation came from the microscopical study of material

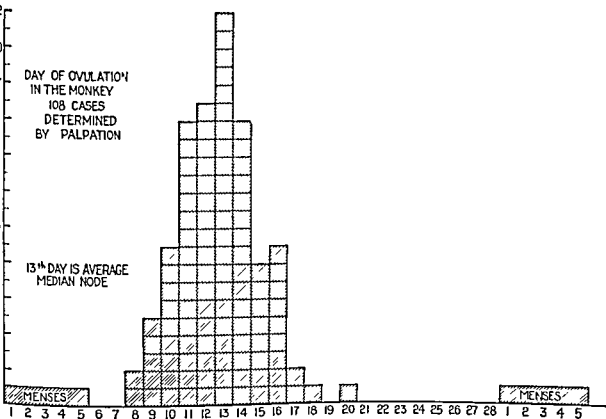


Fig. 26 Graph showing time of ovulation in monkeys (Redrawn from Hartman "Time of Ovulation in Women," courtesy, The Williams & Wilkins Co)

obtained from operations in which removal of the ovaries was necessary. Assessment of the stage of development of the ovarian follicles, or of the age of a corpus luteum, in the light of a known menstrual history, clearly indicated that the time of ovulation was approximately midway between menstrual periods (Fig. 24). Additional evidence pointing in the same direction came later from the recovery of ova from the uterine tubes. Necessarily, such cases have been too few to be conclusive by themselves, but additional data currently accumulating from new lines of work are confirmatory.

The most convincing evidence, because of the possibility of absolute experimental control and surgical checking of the observations, has been obtained from the study of monkeys. Many workers have contributed significantly, conspicuous among whom have been Allen at Yale, and Corner and Hartman at the Carnegie Embryological Institution in Baltimore. Monkeys have such a thin abdominal wall that the size and shape of their ovaries may

be determined with surprising accuracy by bimanual palpation. The bulge on the surface of the ovary caused by the increasing size of an ovarian follicle as it approaches maturity can be felt, and by regular examinations the time at which the enlarging follicle suddenly collapses with the release of its contained ovum can be determined. In such experimental animals, furthermore, absolute confirmation of the findings by bimanual examination may be obtained by operative exposure of the internal organs, by controlled matings, or by careful histological examination of removed tissues. Interestingly enough, the Rhesus monkeys being employed in this line of work have a menstrual cycle of about the same length as that of women. Consequently, the studies carried out on them aid enormously in interpreting the much less complete and less controlled data available for the human female.

From all of these lines of investigation it is becoming increasingly clear that the usual time at which ovulation may be expected to occur is approximately midway between menstrual periods (Fig. 26). It can not be too strongly emphasized, however, that there is great variability in the ovulation time in different individuals. It is impossible to predict that any particular patient will ovulate between the eleventh and fifteenth days of the menstrual cycle, as do the majority of women. Since a knowledge of ovulation time may be of great value in dealing medically with a case of apparent sterility, or as an aid in the proper spacing of pregnancies, the importance of working out practical methods of determining the time of ovulation precisely in the case of a specific individual is self-evident. Equally clear is the folly of attempting to safeguard a patient to whom pregnancy would be dangerous, merely by directing her to abstain from coitus in that part of the menstrual month when most women are known to ovulate. Such a patient may be just the exceptional person who ovulates earlier or later than the average.

Cyclical Changes in Uterine Tubes and Vagina It has been shown by Snyder, Seckinger, and others that the uterine tubes begin to exhibit increased muscular activity at the time of ovulation. This increased activity apparently reaches its height during the three or four days following ovulation while the recently discharged ova are traversing the tube. In the mouse, as shown by Burdick, Whitney, and Emerson (1942), the peristaltic activity is at its maximum in the part of the tube where the eggs are located. There is also at this time an increase in thickness, and apparently in secretory activity, on the part of the epithelial lining of the tube (Fig. 27). It would be interesting to know, in addition, whether or not any increase in the power of the ciliary action of the tubal epithelium occurs at this time, for the cyclical changes in the tube are undoubtedly correlated with the efficient transportation of ova.

In many of the lower mammals there are marked changes in the character of the vaginal epithelium at different ages and at different phases of the sexual cycle. The cyclical changes, particularly conspicuous in some of the rodents, were first reported in detail by Stockard and Papanicolaou for the guinea-pig. Their most striking feature in the guinea-pig or in the white rat, which is now so extensively used for experimental purposes, is a marked increase in the

keratinization of the epithelium at the estrous phase of the cycle, followed by an extensive invasion of the epithelium by leukocytes and desquamation of the surface cells in the metestrous phase of the cycle. This information has been of immense value in the handling of large groups of animals under observation for the effect of some of the hormones involved in regulating the sex cycle. So exactly have these vaginal changes become known and so precisely are they correlated with the changes in the internal sex organs that it is possible for an experienced worker in the field to tell what phase of the sexual cycle an experimental animal is in, merely by microscopic examination of a vaginal smear.

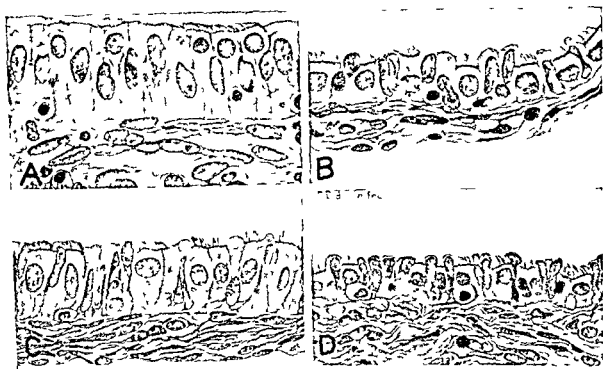


FIG. 27 Epithelial lining of human uterine tube in different states of activity (Drawn $\times 500$, after Snyder, Bull. Johns Hopkins Hosp., Vol. 35, 1924) A, During proliferative phase of uterine cycle B, During secretory phase C, Just before onset of menstruation D, During pregnancy

The age changes occurring in the human vaginal epithelium under hormonal control are very striking. In a nonpregnant, sexually mature woman, the vaginal epithelium is a relatively thick stratified squamous epithelium with a liberal number of flattened cell layers toward its surface (Fig. 28, C). This thick condition of the epithelium can be shown experimentally to depend on the presence of an adequate level of the estrogenic hormone. The young girl (Fig. 28, B) and the senile woman (Fig. 28, D) show a strikingly thinner vaginal epithelium. It is very interesting in this connection that the newborn female infant shows a thick vaginal epithelium (Fig. 28, A) under the influence of estrogenic hormones which enter the fetal circulation by way of the placenta. It is only two to three weeks after birth, however, before this paradoxically thick vaginal epithelium of the newborn is reduced to the thinness characteristic of the period of childhood.

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duction It is not enough that it be brought periodically to maximum efficiency for its own particular rôle, the period of readiness of each part must be so timed that as the critical events in reproduction shift from one organ to another, there is no delay—no essential part of the intricate mechanism unprepared

That the timing of the various events in the sexual cycle is under the control of hormones has long been indubitably established But the interplay of the various hormones involved is intricate It takes much patient experimenting to determine the precise effect of a single hormone acting alone Much more difficult is the interpretation of the effect of several of them acting together or in sequence At the present time there is probably no field in the biological sciences in which investigation is so active as it is in endocrinology Scarcely a current biological or medical journal fails to add some bit, large or small, to the growing mosaic of our knowledge of the mode of production, chemistry, or physiological effects of hormones Nevertheless, it is not yet possible to give even a brief, tentative sketch of some of the major hormonal activities involved in the regulation of the events of the sexual cycle without the reservation that much of the information is recently acquired, not yet thoroughly tested, and therefore subject to revision as new facts come to light

Paradoxically enough, the primary activator is located not in close positional association with the reproductive organs, but deep within the skull, in close association with the brain The pituitary gland, or hypophysis, not much larger than a cherry stone, is an insignificant-looking mass of tissue, the function of which has long piqued man's curiosity In the Middle Ages one readily could have become involved in a controversy as to whether it was the abiding place of the soul, or a special organ for eliminating mucus from the brain Today anyone attempting to interpret the activities of this extraordinarily busy little mass of cells finds himself involved in a whole series of controversies involving anywhere from five to fifteen hormones, most of which pass under several aliases

Long before sexual maturity, the anterior lobe of the hypophysis, through one of the hormones it produces, begins to exert a profound influence on the sex organs If young animals are hypophysectomized, the reproductive organs remain infantile in size, the characteristic sexual cycle is not established, and the individual is sterile Of course it has long been known that early removal of the ovaries resulted in failure of the menstrual cycle to be established, and that their removal during maturity caused cessation of menstruation, but we now begin to see that the chain of events reaches farther back Before the ovary can play its rôle in activating the uterus, it must first be brought to full functional capacity by being itself stimulated during its growth period by a hormone from the anterior lobe of the hypophysis

This early action of the hypophysis is but the beginning of the story After sexual maturity is attained there are hormones produced in the hypophysis that exert a profound effect on the gonads and are, therefore, called

The changes in the character of adult human vaginal epithelium at different phases of the menstrual cycle are not so clear-cut as are the corresponding changes in the rodent. The changes as indicated by smear preparations are, nevertheless, of a similar character. As the time of ovulation approaches, there is a marked decrease in the number of white blood corpuscles appearing in smears along with the desquamated epithelial cells. When ovulation is imminent, the smears will often show keratinized epithelial cells with few or

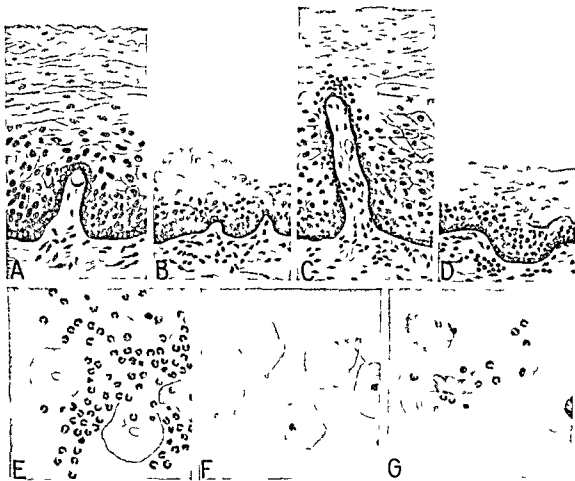


FIG. 28 Vaginal changes occurring under influence of estrogenic hormone. A-D, Sections of vaginal epithelium, $\times 200$ (A) Newborn, (B) infant of two weeks (C) sexually mature adult, (D) senile. E-G, Vaginal smears from adult at different times in the ovulatory-menstrual cycle (Redrawn after Papanicolaou, *Am. J. Anat.*, Vol 52, Suppl., 1933.) (E) Shortly after cessation of menstruation, (F) at about the time ovulation is due to occur, (G) shortly after ovulation.

no leukocytes (Fig. 28, F), much as they do in rodents. In women, however, there appears to be too much individual variability in the character of the smears to permit using the method with assurance as a basis for determining the precise time in the cycle when a particular patient ovulates.

Hormonal Regulation of Sexual Cycle From even a cursory survey of the cyclical changes exhibited by the various parts of the female reproductive mechanism it is evident that the recurring changes must, in some manner, all be co-ordinated with each other. Each organ has its part to play in repro-

of this follicular hormone into experimental animals which have ceased to show estrous changes following complete ovariectomy will re-establish the typical estrous reactions. It is, for this reason, often spoken of as an estrogenic hormone.¹ The significance of the increasing amount of this hormone which is mobilized as follicles become turgid with contained fluid and approach the time of rupture and discharge of ripe ova is self-evident. Events are timed in such a manner that the maximal amount of the hormone inciting to sexual activity is present in the system at the time when fertilizable ova are due to be liberated (Fig. 29).

Following the discharge of an ovum from a follicle, another team of hormones becomes active. The luteinizing hormone from the anterior lobe of the pituitary causes the lining cells of the ruptured follicle to proliferate rapidly and to change their chemistry, with the resultant formation of the corpus luteum. The corpus luteum, in turn, under the additional stimulation of the lactogenic hormone, produces a hormone which acts on the uterus. This hormone is known as progesterone, because it stimulates the mucosal lining of the uterus to undergo the changes preparing it for gestation (Fig. 29). The interesting element of timing again appears conspicuously, for the chain of events which leads up to the preparation of the uterus to receive the embryo was started when the follicle which produced the ovum for fertilization first began to mature.

In the light of this sequence of events the time relations between ovulation and menstruation take on added significance. If ovulation took place, say, on the thirteenth day of the menstrual cycle, and a fruitful coitus occurred at about the same time, it would take the fertilized ovum about 10 days to grow to such a condition that it could successfully implant itself in the uterine lining. In this 10 days, under the influence of the corpus luteum hormone, the uterine mucous membrane is becoming thickened, its glands are becoming active, and its blood supply is becoming increasingly rich (Figs. 23, 24, 29). It is just when the uterus is in this premenstrual phase that it is ideally prepared to receive and embed a young embryo.

The hormone from the corpus luteum appears to have another important physiological effect in addition to its influence on the uterus. The injection of corpus luteum extract has been shown repeatedly to inhibit ovulation. This effect is entirely consistent with the time relations between the maximal development of the corpora lutea of ovulation and the other events of the cycle. Corpora lutea attain a marked degree of development and give every histological indication of active secretion a few days after the rupture of the follicles from which they are formed. They begin to exhibit retrogressive changes on microscopical examination at the time the succeeding menstrual

¹ There are a number of other closely related chemical substances which have a similar physiological action and are therefore called estrogens—e.g., estrone and estrinol, which are recoverable from the urine and which presumably originated from estradiol which was modified slightly within the body before its excretion. The synthesized product diethylstilbestrol, because it acts in a manner similar to these natural estrogens, is included in the same category.

gonadotropic hormones to distinguish them from other hormones of hypophyseal origin which exert specific effects on other organs, such as the thyrotropic and adrenocorticotrophic hormones. It is at present believed that there are two gonadotropic hormones, one of which is called the follicle-stimulating hormone, and the other the luteinizing hormone (Fig 29) Laboratory

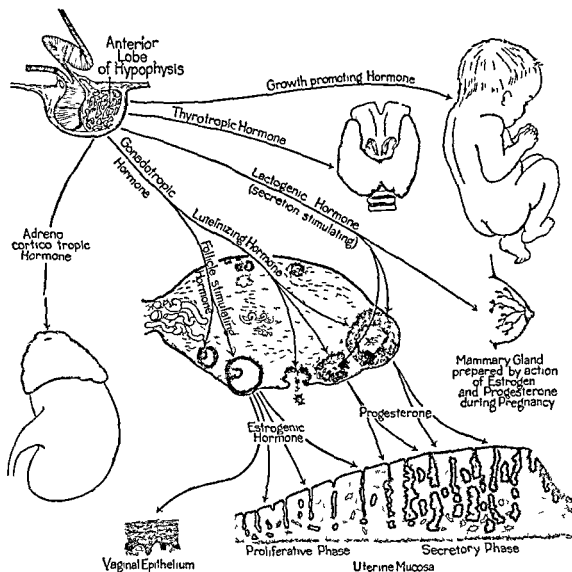


FIG 29 Diagram indicating some of the hormones arising in the anterior lobe of the hypophysis, with especial emphasis on those involved in regulating the cyclic activities of the female reproductive organs

parlance seems to have been corrupted by the alphabetical argot currently being applied to governmental agencies, for these hormones are commonly referred to as FSH and LH, respectively

The follicle-stimulating hormone appears to be concerned with activating successive crops of ovarian follicles to grow and mature. And here appears another link in the chain of hormonal action, for when the follicles commence to enlarge they begin to produce a hormone which can be recovered from the liquor folliculi. This hormone is estradiol. Injection of adequate amounts

after about 30 hours in the female genital tract, while their motility lasts up to about two days. Comparable data for human spermia are far less precise. The best qualified opinion places their retention of fertilizing power at probably about one to two days, with motility persisting for perhaps double that time.

It should be emphasized that these statements refer to sperm in the female genital tract. The length of time sperm may remain alive and retain their ability to fertilize varies greatly under different environmental conditions. In the epididymis and vas deferens of the male, where they remain non-motile, spermatozoa certainly retain their full capacities for many days. Their characteristic power of motility is aroused only when, at the moment of ejaculation, they are mixed with the secretions of the seminal vesicles, the prostate, and the bulbo-urethral glands. That their length of life thereafter depends in large measure on the rate at which they expend their limited store of potential energy is clearly indicated by recent experimental work in artificial insemination. The motility of the spermatozoa in freshly ejaculated semen can be checked by chilling. Under these conditions they do not immediately dissipate their available store of energy. Taking advantage of this fact, the semen of pedigreed stock has been shipped thousands of miles by airplane and introduced into females by means of a syringe, with the successful production of offspring by what might be called "remote control of paternity."

Sperm Transport There still remains much to be learned about the manner in which the spermatozoa make their way from the vagina through the uterus and the uterine tubes. The spermatozoa themselves, of course, are actively motile, swimming in a fluid medium, tadpole fashion, at a rate variously estimated as between 1.5 and 3 mm. a minute. But without some directive stimuli the course of their locomotion is frequently changed and it seems exceedingly doubtful that their own movement alone would account for the arrival of spermatozoa at the upper end of the uterine tubes as promptly as it is known to occur in the case of certain experimental animals. In the rabbit, for example, spermatozoa have been found at the upper end of the uterine tubes three hours after coitus.

There is some evidence suggesting that spermatozoa tend to orient themselves so that they move against a gentle current, thus exhibiting what students of animal behavior call a positive rheotactic response. But even assuming that the downward ciliary current in the uterus is an effective orienting stimulus, as has been maintained by many workers, the time at which spermatozoa reach the ovarian end of the tube is far too short to be accounted for on this basis. Apparently muscular action of the uterus and uterine tubes plays an important part in the prompt arrival of spermatozoa at their destination. At the height of the sexual orgasm in the female there are spasmodic contractions of the smooth muscle of the vagina and uterus. There is some evidence indicating that these contractions may immediately draw some of the freshly deposited semen from the vagina into the uterus. While this may ordinarily be an accelerating factor in sperm transportation it certainly is

period is due to appear, and they have decreased visibly in size by the time a new group of follicles approaches maturity. Such findings point to the corpora lutea of ovulation as the source of a hormone which acts as an antagonist to the follicle-stimulating hormone from the anterior lobe of the hypophysis, thus holding in check the development of the next group of follicles until a period of rest has been enforced.

The events in the sexual cycle have been presented in the barest outline, and with the avoidance, as far as possible, of the many still unsettled points which make this one of the most intriguing fields of current biological investigation. Even this brief sketch, however, should make it apparent how beautifully co-ordinated a mechanism is involved. So far, we have looked only at the series of changes as they recur in anticipation of pregnancy. Ovulation is the critical event in relation to which all the other cyclical changes are timed. When an ovarian follicle ruptures, liberating an ovum ready for fertilization, all the other organs are prepared to play their essential rôles if the ovum is fertilized.

FERTILIZATION

There is perhaps no phenomenon in the field of biology that touches so many fundamental questions as the union of the germ cells in the act of fertilization, in this supreme event all the strands of the webs of two lives are gathered in one knot, from which they diverge again and are rewoven in a new individual life history. The elements that unite are single cells, each on the point of death, but by their union a rejuvenated individual is formed, which constitutes a link in the eternal procession of Life.—T. R. LILLIE, in "Problems of Fertilization."

Sperm Viability. There are many critical events intervening between the formation and liberation of mature gametes and their final fusion in fertilization. The immediate result of coitus is the deposition of semen in the vagina (*insemination*). Thence the spermia must make their way through the uterus and into the upper part of the uterine tubes where fertilization ordinarily takes place. In comparison with the size of the spermia, the distance they must travel is great, and the route may be beset with chemical hazards in the form of abnormally strongly acid secretions or mechanical obstacles such as a crooked and compressed cervical canal or uterine tubes narrowed or occluded by disease. The enormous numbers of spermia contained in an ejaculate of semen (on the average in the neighborhood of 200,000,000) makes it probable that some of them will reach the oviduct while they are still capable of penetrating and fertilizing the ovum.

There has been, and still is, much misinformation current as to the feats of travel and length of life of spermatozoa. The present state of our knowledge does not justify any too dogmatic statements as to the exact length of time that human spermia retain their motility—and, more important, their fertilizing power—but both of these periods are certainly much shorter than formerly believed. Persistence of motility used to be regarded as indicative of fertilizing capacity. We now know that motility lasts much longer than the capacity of carrying out fertilization. In the case of the rabbit, for example, we have good experimental evidence that the spermatozoa lose their ability to fertilize

thickened and less readily penetrated, coincidentally, the remaining spermia appear to lose their directive activity, and soon only scattered ones remain in the neighborhood of the fertilized ovum. That this change is due to the fertilization of the ovum and not to loss of activity on the part of the spermia may be demonstrated readily by adding unfertilized ova to the dish and watching them fertilized by the sperm cells in question.

Only the head of the spermium (which is almost entirely condensed nuclear material) and the neck (containing the centrosomal apparatus) enter the ovum. The tail is dropped off at the time of penetration (Fig 30, B). Once within the ovum, the nuclear material contained in the head of the

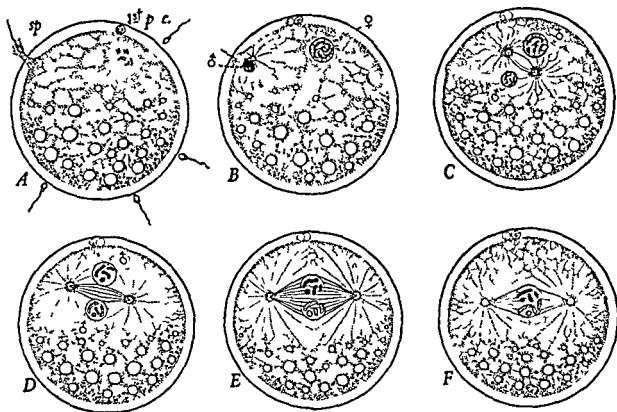


FIG 30 Diagrams schematically illustrating process of fertilization and formation of the first cleavage spindle (After William Patten) As in Fig 19, the species number of chromosomes is assumed to be eight

Abbreviations *sp*, spermium, *p c*, polar cell (polar body) The male and female symbols designate the male and female pronuclei respectively

spermium loses its condensed form and begins to show its chromosomal content. In this condition it is known as the male pronucleus (Fig 30, C).

Generally, in mammals, the first maturation division of the ovum occurs at just about the time the ovum is liberated from the ovary, and the second maturation division is likely to be delayed until the ovum has been penetrated by a sperm cell. Once penetration of the ovum has occurred, however, events move rapidly, and by the time the male pronucleus has been formed the second maturation division of the ovum has been completed. The reduced nucleus of the ovum is then known as the female pronucleus. Fertilization can be said to have occurred when the chromosomes from the male and female pronuclei become aggregated together (Fig 30, E, F). As each

not an indispensable one for there are innumerable well-authenticated cases, both clinical and experimental, of pregnancy occurring in the absence of orgasm on the part of the female. In such instances the entrance and traversing of the uterus must depend primarily on the activity of the spermatozoa themselves.

Mention has already been made of the heightened muscular activity of the tubes at the time of ovulation. On the basis of recent studies it seems probable that this increased activity is important in sperm transportation as well as in the journey of the ova toward the uterus. Careful observation of the activity of surgically exposed tubes in living experimental animals indicates that temporary rings of contraction tend to divide the tube into a series of compartments. At any given moment in any compartment, the downward beating cilia along the outer walls tend to create also central back eddies. In such currents and counter-currents the spermatozoa in the lumen of the tube would be scattered rapidly throughout the area between two adjacent contraction rings. When the zones of contraction relax at one level and form at another, some spermatozoa would be crowded back toward the uterus but others would find themselves in a new compartment nearer the ovary. The formation and reformation of such compartments by temporary rings of contraction at shifting levels would rapidly disperse the spermatozoa throughout the length of the tube.

Union of Gametes The growth, the maturation, and all the factors leading toward the meeting of the male and female sex cells are but preliminary to their actual fusion. It is the penetration of the ovum by a spermatozoon and the resultant mingling of the nuclear material each brings to the union that constitutes the culmination of the process of *fertilization* and marks the initiation of the life of a new individual. Direct observations of the actual union of the gametes in mammals have been few and fragmentary. Nevertheless, interpreting these observations in the light of the much more detailed information available from the study of water-living forms where fertilization normally occurs outside the body of the mother, it is possible to piece out a fairly circumstantial story of the main events.

Assuming that the coitus of healthy individuals occurred near the time of ovulation, it would be but a matter of a few hours before the ovum entering the fimbriated end of the uterine tube would be surrounded by large numbers of active spermatozoa. However great the numbers present, normally only a single spermatozoon enters the ovum (Fig. 30 A). As soon as it has been entered by a sperm cell an ovum appears to undergo immediate changes which tend to prevent other spermia in its neighborhood from penetrating it. This phenomenon may readily be observed in many marine forms where fertilization can be carried out in a dish of sea water under the microscope. When the spermia are first introduced into a dish containing ova one sees swarms of them surrounding each ovum. Even the relatively enormous bulk of the egg cell may actually be set in rotation by their combined activity. Abruptly, when one spermium has penetrated the ovum, its surface membrane becomes

of chromosomes, making a species number of 48. We can say that the male chromosomal number is 23 pairs of similar somatic chromosomes plus a twenty-fourth dissimilar pair composed of an X and a Y chromosome, and that the female chromosomal number is 23 pairs of somatic chromosomes plus

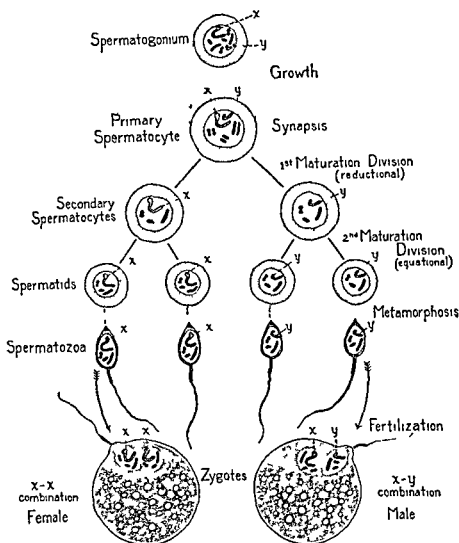


FIG. 31 Schematic diagram showing separation of the members of the sex chromosome pair in maturation, and their recombination in fertilization. It is assumed that the species number of chromosomes is eight and that it is the male which produces gametes of different potentialities with regard to sex determination. The sex chromosomes are stippled, other chromosomes are drawn in solid black.

a twenty-fourth balanced pair consisting of an X chromosome associated with another X chromosome in the place where the male showed a small Y chromosome.

Careful studies of maturation have yielded the clue as to how this sex difference in chromosomal pattern comes about and is maintained. In the synapsis which occurs in the maturation divisions, the two members of the sex chromosome pair, as is the case with any other chromosomal pair, will be found associated with each other. In the reduction division which separates the members of the chromosomal pairs in the spermatocytes of the male,

pronucleus contributes half the species number of chromosomes, the full species number of chromosomes is re-established in the fertilized ovum

During the period between the penetration of the ovum by the spermium and the mingling of the chromosomes from the two pronuclei, a mitotic spindle has been forming from the centrosomal apparatus brought in by the spermium (Fig 30, C, D) On this spindle the chromosomes contributed by both parents become arranged preparatory to the first mitotic division in the growth of the new individual (Fig 30, E, F) This first cell division ordinarily follows closely after the fusion of the pronuclei, but the mechanism of activation is exceedingly complex and its precise nature remains unknown There is evidently far more than the mere union of male and female pronuclei involved, for in some of the lower animals having gametes which lend themselves readily to experimental procedures, spermatozoa can be made to start division in the cytoplasm of eggs from which the nucleus has been removed In other instances a spermatozoon, the nuclear material of which has been fatally damaged by exposure to radium, may still penetrate an ovum and cause it to start dividing Furthermore, the ova of many of the lower forms of animals can be made to develop in the absence of spermatozoa by appropriate mechanical or chemical stimulation—a process known as artificial parthenogenesis As a rule, however, in such cases development seems to lack its normal vigor and to proceed but a short way The impetus to the initial cell division is present but the full parental contribution necessary for the maintenance of vigorous normal growth is lacking

Sex Determination Probably no embryological question has been the subject of so much conjecture as sex determination From time immemorial, theory after theory purporting to explain why this embryo became a male and that one a female has been advanced, only to be discredited Under such circumstances, one naturally becomes exceedingly cautious in discussing any theory in this field At the present time, however, there is so much interest in the chromosome theory of sex determination that anyone who would consider himself well informed biologically must be familiar with it, regardless of its ultimate fate

In discussing maturation, it was stated that the chromosomes present in the cells of a species could be arranged in pairs, the members of which were alike (Fig 21, A) In a male individual, however, one pair of chromosomes is an exception in that its members are strikingly unlike (see the pair at the extreme right in Fig 21, A) The members of this pair are called the "X" and "Y" chromosomes Although our knowledge is as yet fragmentary and unsatisfactory, there is sufficient evidence indicating that the X-Y pair of chromosomes is associated with the determination of sex, so that they are commonly referred to as "the sex chromosomes" If the cells of a female individual are examined with reference to this peculiar pair of chromosomes, we find instead of the large X and the small Y members characteristically appearing in the male that the female has two large X members We can then amplify our previous statement that the cells of human beings have 24 pairs

4

Cleavage, Germ Layers, and Establishment of Embryonic Body

CLEAVAGE

Fertilization precipitates in the ovum a series of cell divisions which follow one another in close succession. The way in which these so-called cleavage divisions are carried out varies in different groups of animals in correlation with the amount of yolk stored in the ovum as food material for its growth needs. The yolk, being nonliving and inert, plays no active part in cleavage, which must be carried out by the living protoplasmic portion of the cell, but it does exert a local retarding effect by the mechanical impediment it offers to the process. Consequently, in such eggs as those of amphibians or birds where the yolk content is large, its presence complicates the pattern assumed by the daughter cells during cleavage. In the ova of all the higher mammals the amount of stored food material is exceedingly small, correlated with the fact that the embryo at an early stage in its development draws upon the uterine circulation of the mother for its nutrition. For this reason, the cleavage of mammalian ova reverts to the simple (holoblastic) type seen in very primitive forms having ova with a scanty and uniformly distributed (isolecithal) yolk content (Fig. 32).

Cleavage in Primate Ovum Although the cleavage stages of the human ovum have not as yet been observed, there is every reason to believe that they differ in no essential from the corresponding stages in other mammals with similarly organized ova. In fact, in all the higher mammals so far studied, the cleavage pattern is strikingly similar. The cleavage divisions in the monkey ovum, recently studied in great detail in living eggs reared by tissue-culture methods, probably parallel very closely the corresponding stages in man, and have, therefore, been used to fill this gap in our direct knowledge of the earliest steps in human development.

In dealing with a spheroidal cell such as an ovum, some criterion of orientation is most helpful. Ova which have a large amount of yolk aggregated at one pole offer no difficulty in this respect. The pole at which the yolk is concentrated may be designated as the "vegetative pole," and the opposite pole, where the nucleus and most of the unmodified cytoplasm lie, may be called the "animal pole." No such clearly marked polarity exists in the ova of the higher mammals because the stored food material is minimal in amount.

the X chromosome must inevitably go to one cell and the Y chromosome to another. In the equational division each daughter cell will give rise to another cell precisely like itself as to chromosomal content. So the end-result of the two maturation divisions of each primary spermatocyte is the production of two spermatozoa having 23 somatic chromosomes plus an X chromosome, and two which have 23 somatic chromosomes plus a Y chromosome. Since in all the cells of the female there is an X-X combination, in the reduction division which occurs in the maturation of the ova one of the X chromosomes must go to the polar body and one to the maturing ovum, so the chromosomal formula for all ova will always be 23 somatic chromosomes plus an X chromosome.

When an ovum ready for fertilization is surrounded by swarms of spermatozoa, half of which have one chromosomal pattern and half another, it is obvious that there are equal chances as to which of the two types will be the one first to penetrate the ovum. If it is a sperm cell carrying an X chromosome, fertilization will establish in the zygote the X-X combination characteristic of the female. If, on the other hand, the successful sperm cell carried a Y chromosome, the X-Y combination characteristic of the male would result. If, for the sake of simplicity in diagramming, we use germ cells from an animal having a species number of only eight chromosomes, the essential happenings as postulated by the chromosome theory of sex determination may be schematically summarized as indicated in Fig. 31.

Perhaps the fairest way to assess this particular theory as to the determination of sex is to say that at the present time it accords with more of the known facts than any other theory. We must recognize, however, that as yet we know practically nothing as to the mechanism by which the characteristically different chromosomal pattern present in the two sexes may operate. There is some indication that the chromosomal combination established at the time of fertilization may provide merely the initial impetus toward sexual differentiation in one direction or the other, and that the action of certain internal environmental factors may be important in bringing about full differentiation.

From the standpoint of dealing with patients seeking advice as to the possibility of the control of the sex of their offspring, it is clear that only one honest answer is possible. So far as is known, the matter of the sex of a child is fortuitous and is entirely beyond our power to control in any manner now known. To promise to influence the issue is to place oneself in company with the medicine men of primitive tribes, or to brand oneself as a charlatan.

4

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and fairly uniformly distributed as minute lipid droplets in the cytoplasm. The point at which the polar bodies are liberated is, however, probably homologous with the so-called "animal pole" of heavily yolked eggs, and may be used to serve as an orientation point in discussing the planes of the early cleavage divisions.

In mammals, as is the case with surprising uniformity throughout the animal kingdom, the mitotic spindle of the first cleavage division forms at right angles to an imaginary axis passing through the ovum from animal to vegetative pole. The plane of separation between the resulting *blastomeres*, as

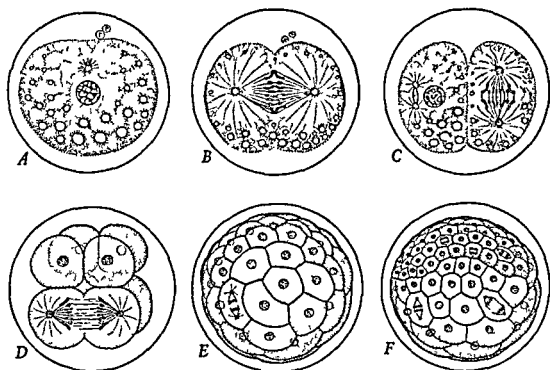


FIG. 32 Cleavage in an egg having but a small amount of yolk in the cytoplasm (After William Patten). Note that the blastomeres are separated from each other promptly and completely.

the daughter cells are called, lies in the equator of the spindle, and therefore coincides with the imaginary axis of the ovum as established by the point at which the polar bodies were liberated (Fig. 32, B, C).

Mitotic spindles for the second cleavage divisions are formed in the first two blastomeres shortly after their establishment. One of the blastomeres usually divides a little sooner than its mate, so there is a transitory three-cell stage (Fig. 33, B) before the characteristic four-cell stage is reached. The spindles for these second divisions form at right angles to the first and to each other, so that the characteristic four-cell stage has the configuration of crossed dumb-bells (Fig. 33, C).

Further cleavage divisions follow one another in an orderly series, but in less precise orientation. So rapid is their succession that the growth interval which ordinarily supervenes between succeeding mitoses is curtailed. In consequence, there is at first no growth in the cell mass as a whole and the indi-

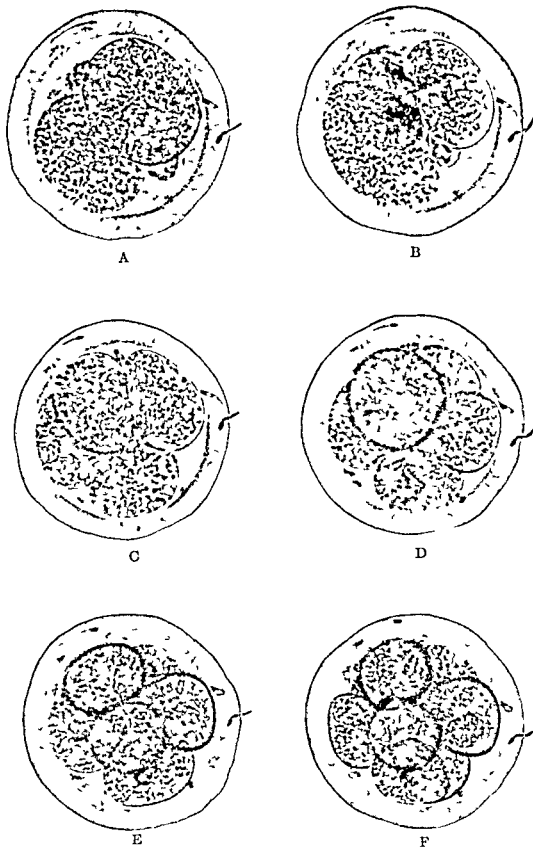


FIG 33 Photomicrographs ($\times 300$) of living monkey ovum showing its cleavage divisions (After Lewis and Hartman, *Carnegie Cont to Emb*, Vol 24, 1933) The fertilized ovum was washed out of the tube, cultivated in plasma, and its growth changes recorded as micromoving pictures The illustrations are enlargements from single frames of the film A, Two cell stage, about $29\frac{1}{2}$ hours after ovulation B, Three-cell stage, about $36\frac{1}{2}$ hours after ovulation C, Four-cell stage, about $37\frac{1}{2}$ hours after ovulation D, Five-cell stage, about $48\frac{1}{2}$ hours after ovulation, E, Six-cell stage, about 49 hours after ovulation F, Eight-cell stage, about 50 hours after ovulation (A seven-cell stage lasting but three minutes intervened between the six- and eight-cell stage)

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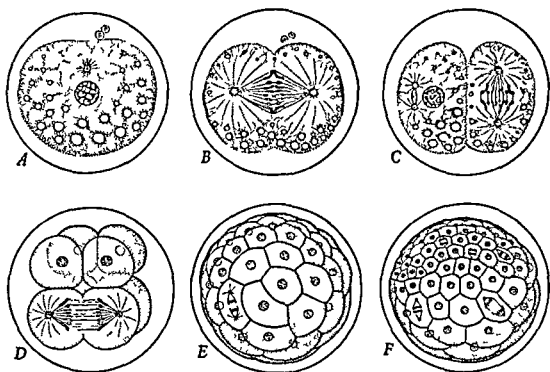
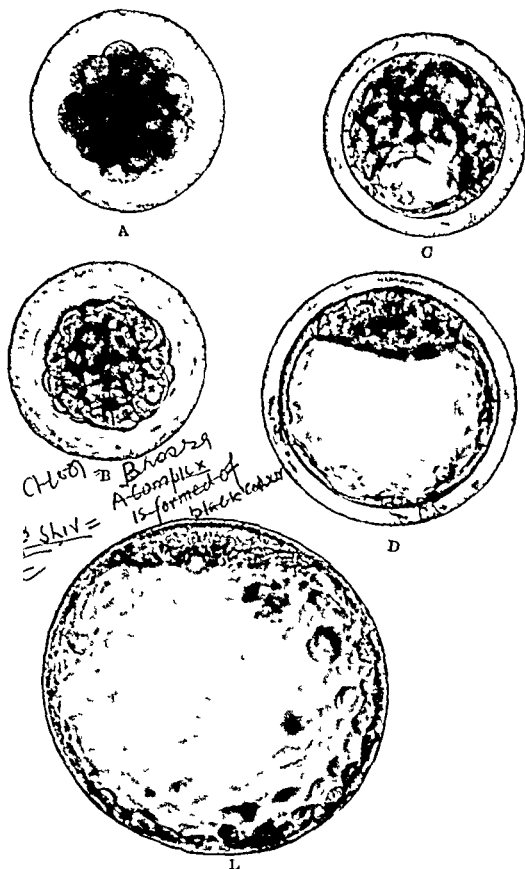


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FIG 34 Photomicrographs ($\times 250$) of living rabbit embryos in the morula and blastula stages. The temporary gelatinous layer shown outside the zona pellucida in Gregory's original photographs has been omitted in this illustration. A, Morula, 55 hours after coitus. B, Morula, 71½ hours after coitus. C, Beginning of transformation of morula to blastula, 76½ hours. D, Central cavity more marked—peripheral cells flattened against zona pellucida, 90 hours. E, Characteristic blastula stage, 92 hours. (After Gregory, Carnegie Cont. to Emb., Vol. 21, 1930)

vidual blastomeres after each succeeding division become smaller and smaller (Fig 33, A-F) Since the zona pellucida persists intact throughout the period of cleavage, the blastomeres are forced to dispose themselves within its spheroidal cavity After several cleavage divisions have taken place, the resultant blastomeres appear much like a solid ball of cells suggestive of a mulberry The embryo in this condition is said to be in the *morula*, i e, "little mulberry," stage (Fig 34, A)

DIFFERENTIATION OF BLASTODERMIC VESICLE

After a characteristic morula has been formed, the term cleavage is not ordinarily applied to the cell divisions which occur The implication should not be drawn that cell division ceases or even that it is retarded in rate On the contrary, it continues with unabated rapidity But processes of segregation and differentiation, even thus early, begin to make their appearance, and the term cleavage, which implies merely an increase in cell numbers through repeated cell divisions, ceases adequately to characterize the processes of regrouping and divergent specialization which now begin to make their appearance While each cell division seems to pass on to each daughter cell a scrupulously divided share of the chromatin which was the dowry of the fertilized ovum from the parents, subtle sorting-out processes are already at work "To say that the daughter cells make an uneven division of their heritage is, of course, a crude way to state it To say anything more precise at the present time would be highly speculative" (Streeter, 1931, p 497) But, as we trace development beyond the cleavage stages, the regroupings of specialized cell masses which unfold into definite organs testify to the existence of a sorting-out process we can not as yet analyze

When the blastomeres of a morula begin to be rearranged and organized about a central cavity (Fig 34, B-E), we say that the morula is becoming a *blastula* or that the embryo is entering the blastodermic vesicle stage¹ It is during this phase of development that the restraining zona pellucida disintegrates and the rapid growth of the embryo in size first begins The newly formed central cavity is called the segmentation cavity or *blastocoele* (Figs 34, C-E, 35, A-C) The large size of the blastocoele in mammalian embryos of this age has a dual significance Phylogenetically, this now fluid-filled space represents the place where ancestral types carried a dowry of food in the form of yolk Ontogenetically, as we so often see in embryology, the outgrown plan persists and is adapted to new conditions The yolk space is retained and increased in size as more and more fluid accumulates within it, thereby expanding the outer layer of the blastocyst into a voluminous membrane which later becomes a means of drawing food for the yolkless embryo from the uterine circulation of the mother For this reason, the layer of cells which con-

¹ Terms designating "stages of development" are convenient in discussing the progress of events and the relative uniformity which has gradually been established in their usage is a great aid to mutual understanding It should be borne in mind however that the delimitation of "stages" is purely arbitrary, for development is a continuous process and one phase merges into another without any real point of demarcation.

occurs during the journey of the ovum through the tube to the uterus. The minuteness of the newly fertilized ovum makes its recovery from among the folds of the tubal lining exceedingly difficult. In animals, excision of the tube followed by its irrigation and a search of the washings under a binocular microscope frequently leads to the recovery of the ovum. Recently human ova have been recovered by a modification of this technic in which the uterine tube was washed out in the course of a pelvic operation, by means of a stream of sterile saline solution from a syringe inserted into the uterine lumen. Unfortunately, none of the few human ova thus recovered have been in the cleavage stages, all of them have been unfertilized ova in which signs of degeneration were already evident.

The formation of the blastodermic vesicle occurs in the uterus before the embryo is attached to the uterine lining. Recovery of embryos from the uterus during this phase of their development presents the same sort of difficulties as their recovery from the uterine tubes. Once an embryo has attached itself in the uterine mucosa the chances for its recovery are increased. In the monkey, it is known definitely that the embryo is just attaching itself to the surface of the mucosa on the ninth day, and that the burrowing of the embryo into the uterine mucosa follows rapidly within the next 20 to 30 hours. As yet there is little available human material showing the early phases of implantation. The exceptionally well preserved young human embryos secured recently by Hertig and Rock are our best source of information. Regrettably their youngest specimens were not available in time to be illustrated in this chapter. In the light of the careful clinical histories available in connection with them, it would appear that human implantation probably occurs on the 8th day.

FORMATION OF GERM LAYERS AND ESTABLISHMENT OF EMBRYONIC BODY

In dealing with the structure of embryos in the state of development of the earliest human embryos, before familiar body landmarks and organs appear, it is helpful to analyze them in the terms of the three primary germ layers. These layers are (1) the ectoderm, which, as its name implies, forms the outer covering of the embryo, (2) the entoderm which lies deep to the ectoderm and forms the lining of the primitive gut cavity, and (3) the mesoderm, which develops between the ectoderm and entoderm. In the youngest known human embryos these germ layers are already partially differentiated. To understand their relations, therefore, we must again have recourse to conditions in other mammals. Such an approach would undoubtedly be desirable even if a complete series of young human embryos were available, for the fragmentary material at our disposal clearly indicates that the germ layers in man arise in a much abbreviated manner. To speak figuratively, it is as if the human embryo, realizing the longer path of differentiation it must travel, impatiently hurries through these early stages in its development. Once established, however, the general scheme of arrangement of its germ

stitutes the outer wall of the blastocyst is called the *trophoblast* or *trophectoderm* (Fig 35, C)

In the formation of the distended blastodermic vesicle an internal cluster of cells is established at one pole. This, for want of a better term, has been called the "inner cell mass" (Fig 35). Although it can not be carried through in all details, the general distinction may be made that the inner cell mass is destined to be concerned primarily with the formation of the embryonic body,

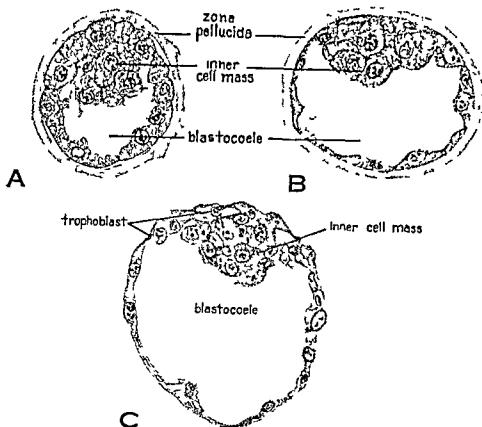


FIG 35 Three stages of the blastodermic vesicle (blastocyst) of the pig, drawn from sections to show the formation of the inner cell mass A, B, From embryos in the Carnegie Collection, C, after Corner—all $\times 375$ (A) Removed from uterus of sow four and three fourths days after copulation (B) Copulation age six days, one and three-fourths hours (C) Copulation age, six days, 20 hours

whereas the thin outer wall of the blastodermic vesicle contributes, not to the make-up of the embryo, but to the formation of protective and trophic membranes which are developed into the fetal part of the placenta

As was the case with the cleavage stages, the early blastodermic vesicle stages have not been observed in human material. Nevertheless, the fundamental similarity of these stages in all the other mammals in which they have been studied makes reasonable the inference that the human blastula stages would closely parallel those used as a basis for the foregoing outline of this phase of mammalian development. The reasons for the failure to secure human embryos of such ages are quite obvious. Fertilization normally takes place in the uterine (Fallopian) tube near its fimbriated end, and cleavage

appearance and soon come to constitute a second complete layer inside the original outer layer of the blastocyst (Fig 36, B, C) The internal lumen bounded by the entoderm is known as the *primitive gut (archenteron)* At a later stage we shall see folding processes separate this primitive gut into a portion

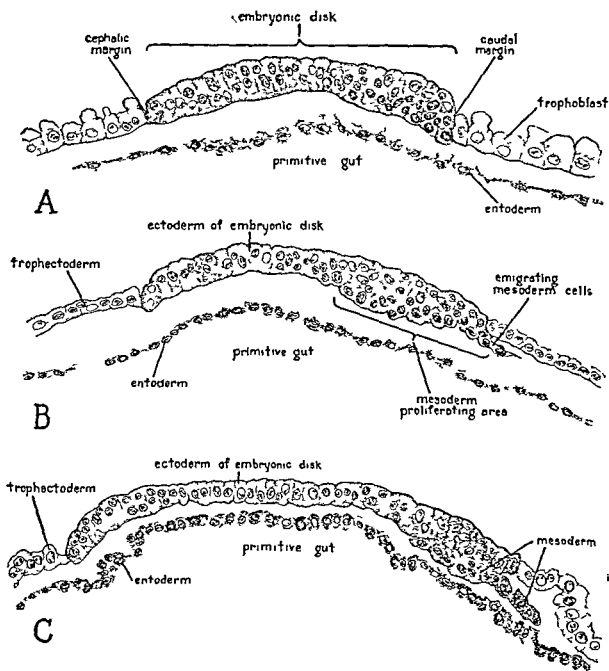


FIG 37 Longitudinal sections of the embryonic disk of the pig during the ninth day of development showing three stages in the origin of the mesoderm (Projection drawings ($\times 225$) from sections of embryos in the Carnegie Collection)

inclosed within the embryonic body to form its gut tract, and a distal sac communicating with the embryonic gut mid-ventrally and known as the yolk-sac. Meanwhile, the mass of cells remaining after the emigration of the entoderm cells of the yolk-sac becomes more regularly arranged and is known as the *embryonic disk*

layers is fundamentally the same in plan as that exhibited by more primitive forms

Of the mammalian forms which might be used as an aid to interpreting conditions in young human embryos, the pig is perhaps as useful as any. Exceptionally complete series of young pig embryos have been collected and the material has been critically studied. Moreover, in the pig the early stages in the formation of the germ layers and the extra-embryonic membranes are

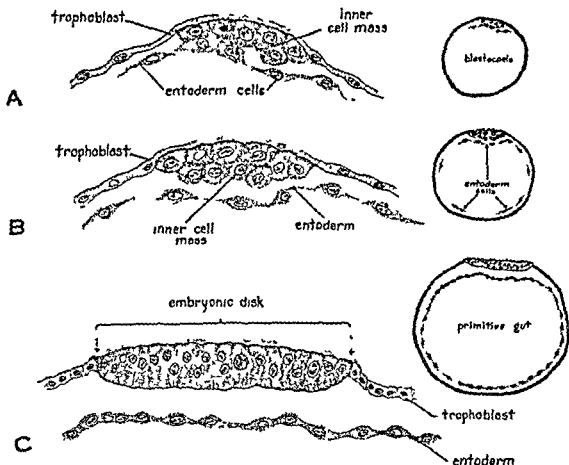


FIG. 36 Sections of pig blastocysts showing the first appearance and subsequent rapid extension of the entoderm (From embryos in the Carnegie Collection) (Left) Detailed drawings of inner cell mass, $\times 375$ (Right) Sketches of same sections entire. The approximate age of the embryos represented ranges from seven to eight days

carried out in more leisurely fashion and with less telescoping of one process into another than is the case in many other mammalian types. Let us, therefore, digress for the moment from young human embryos, and try to acquire some collateral information which should be of assistance in understanding their structure.

Formation of Entoderm The blastodermic vesicle of the pig looks much like that of the rabbit (cf Figs 34, 35). Shortly after the vesicle has become conspicuously enlarged, some of the cells become detached from the inner cell mass and push out into the blastocoele (Fig 36, A). These are the first of the entoderm cells. They are increased in numbers very rapidly after their first

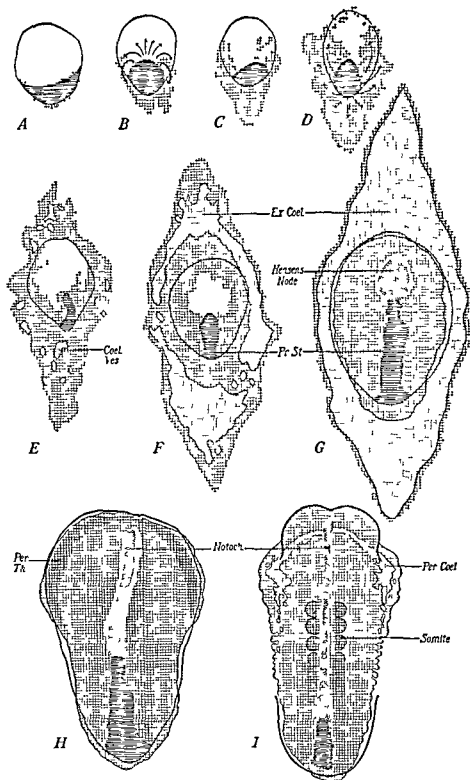


FIG 38 Diagrams showing origin, extension, and early differentiation of the mesoderm in a series of pig embryos ranging from about the ninth to the fifteenth day of development (After Streeter, slightly modified)

In each illustration the embryo is supposed to be viewed in dorsal aspect as a transparent object. Except for outlining the embryonic area, only mesodermal structures are represented. The area indicated by heavy horizontal hatching in A is the thickened part of the embryonic disk from which mesoderm is first proliferated.

Formation of Mesoderm and Origin of Primitive Streak Not long after the entoderm is established, a local differentiation occurs in the embryonic disk which presages the formation of the mesoderm. Sections through the disk show at one part of its margin a heightened rate of cell proliferation accompanied by a definite increase in thickness (Fig 37, A, B). Interpreting this thickening in the light of later developments, it is possible for us to say that its appearance definitely establishes the longitudinal axis of the embryo. The thickening occurs at the part of the disk which is destined to become differentiated into the caudal end of the embryo.

In dorsal views of an entire embryo the thickened area when it first appears is crescentic in shape, with its convexity indicating the caudal extremity of the embryonic disk, and its horns spreading out over the greater part of the caudal half of the margin of the disk (Fig 38, A). At this stage of development the embryonic disk apparently undergoes rapid concrescence caudally. That is, while the anterior margin of the disk is spreading out radially in a manner typical of uniform rate and unspecialized direction of growth, the posterior margins grow at an accelerated rate toward a point of convergence at the caudal extremity of the disk. (See arrows in Fig 38, B). This tends at the same time to lengthen the embryonic disk cephalocaudally and to crowd the thickened area more toward the mid-line. Further progress of this convergent differential growth changes the originally crescentic thickened area of the embryonic disk to an oval (Fig 38, D), and then pulls it out into a band lying in the long axis of the embryo (Fig 38, E-G). This thickened longitudinal band is known as the primitive streak. Those who have a background of comparative embryology will recognize the thickened, mesoderm-proliferating crescent which is reshaped by concrescence into the primitive streak as the homologue of the fused lips of the blastopore of more primitive forms.

The change in shape and position undergone by the originally crescentic area of the embryonic disk from which the first mesoderm cells arise in no way retards its activity as a growth center. We find this area, throughout its transformation and later when it has become the primitive streak, still a region of rapid proliferation from which newly formed mesoderm cells are constantly being pushed out. It seems not unlikely that the formation of the depressed area along the center of the primitive streak which is known as the primitive groove is a local structural modification entailed by the rapid lateral emigration from this region of cells which are being added to the expanding sheets of mesoderm (Fig 39, E).

Formation of Notochord Intimately associated with the formation of the general mass of the mesoderm is the origin of an axially located cylindrical mass of cells known as the notochord. The notochord, both phylogenetically and ontogenetically, is of great morphological importance. In the most primitive of the vertebrate group it is a well-developed fibrocellular cord lying directly ventral to the central nervous system and constituting the chief axial supporting structure of the body. In fishes such as those of the shark family

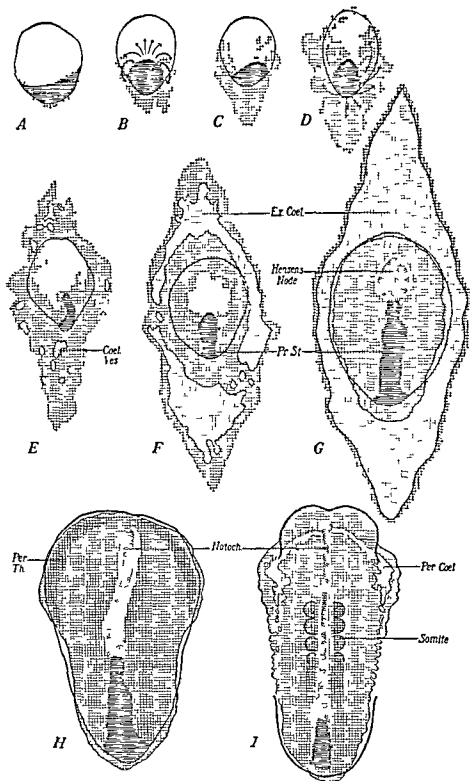


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In each illustration the embryo is supposed to be viewed in dorsal aspect as a transparent object. Except for outlining the embryonic area, only mesodermal structures are represented. The area indicated by heavy horizontal hatching in *A* is the thickened part of the embryonic disk from which mesoderm is first proliferated.

(elasmobranchs), ringlike cartilaginous vertebrae are formed about the notochord. Although somewhat compressed where the vertebrae encircle it, the notochord persists in such forms as a well-defined continuous structure extending throughout the length of the vertebral column. When, in the progress of evolution, cartilaginous vertebrae are replaced by more highly developed bony vertebrae, the notochord is still more compressed. But even in the higher mammals a minute canal in the centra of the vertebrae still remains to mark its existence, and the central portion of the nucleus pulposus of the inter-

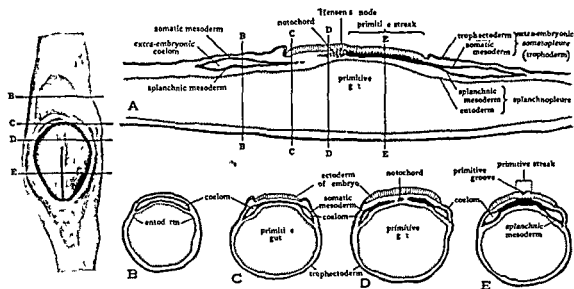


FIG. 39 Drawings to show structure of pig embryos in primitive streak stage. A, Sagittal section. B-E, Cross-sections at the levels indicated on the drawing of the entire embryo at the left, and on the drawing of the sagittal section above. In this and in many of the subsequent figures which represent sections of young embryos the interrelations of the primary germ layers are emphasized by the use of distinctive conventional shading. In this scheme the ectoderm is closely hatched, the coherent layers of the mesoderm are represented in solid black, and scattered mesenchymal cells are shown as coarse angular dots. In younger embryos the endoderm is represented as a fine line bordered by a row of round dots, as in this illustration and in Figs. 49, 70. In older stages the entodermal lining of the gut tract becomes sufficiently thickened so that it is preferable to represent it by suggesting the columnar character of its cells (See, for example, Figs. 56, 69.)

vertebral disk is clearly a notochordal remnant. In the early stages of development, the notochord of a mammalian embryo is a conspicuous structure, at once a record of evolutionary history and an advance indication of the location of the vertebral column.

Embryologically, the notochord in all the higher vertebrates arises in essentially the same manner. The cells of which it is composed take their origin from a thickened mass of rapidly proliferating cells (*Hensen's node*) at the anterior end of the primitive streak. Pushing cephalad from this growth center, these cells become molded into a characteristic rod-shaped mass situated medially in the growing embryo. The sheetlike masses of mesoderm arising from the primitive streak, in their peripheral spread, seem to leave a

temporarily vacant area just cephalic to the primitive streak, and it is into this unoccupied area that the notochord grows (Figs 38, G, H, 39, A, D)

There has been some divergence of views among embryologists as to the interpretation to be placed on the origin of the notochord. A book of this type does not seem the place to enter into such controversies which are deeply rooted in comparative embryology. Suffice it to say that, with due recognition of the existence of alternative views, the notochord will in this text be treated as belonging with the mesoderm. This is logical and convenient on the basis of its position between ectoderm and entoderm, its supporting function in the body, and its intimate association with the connective tissues. Furthermore, its origin as an outgrowth from Hensen's node is quite in line with the origin of the rest of the mesoderm. Hensen's node is essentially a knot of rapidly proliferating cells at the cephalic end of the primitive streak. The mesoderm, it will be recalled, is derived from the rapidly proliferating mass of cells at the caudal end of the embryonic disk which becomes reshaped to form the primitive streak, and, after this reshaping, continues to push out more mesoderm cells into the layers already started. The notochord arises from the cephalic part of this same mass of proliferating cells and grows, as does the rest of the mesoderm, between ectoderm and entoderm. It differs in origin from the rest of the mesoderm only in starting a little later in point of time and being more circumscribed in its growth direction and more definite in shape and extent.

Growth and Early Differentiation of Mesoderm During the time in which the notochord is being formed, the main mass of the mesoderm continues to spread out peripherally from the primitive streak and soon extends far beyond the region of the embryonic disk. We then distinguish that part of the mesoderm underlying the embryonic disk as intra-embryonic and that part of it which extends peripherally to line the blastodermic vesicle and to reinforce the amnion and the yolk-sac as extra-embryonic. This distinction is one of convenience in description, but, as applied to very young embryos, it is entirely arbitrary, for there is at first no line of demarcation between the two areas. It is helpful, however, to realize at the outset that these peripheral layers of the mesoderm—together with the trophoblast, the amniotic ectoderm, and the yolk-sac entoderm—go into the fabrication of protective and trophic membranes which envelop the growing embryo. The fact that they are not incorporated in the embryonic body but discarded at the time of birth is implied in their designation as extra-embryonic membranes.

The rapidly growing mesoderm does not remain long undifferentiated. Sections of slightly older embryos show the lateral portions of the mesoderm splitting into two layers (Figs 39, D, E, 49, F). The outer layer is called the *somatic mesoderm* and the inner layer the *splanchnic mesoderm*. The cavity between somatic and splanchnic mesoderm is the *coelom*. Because the somatic mesoderm and the ectoderm are closely associated and undergo many foldings in common, it is frequently convenient to designate the two layers together by the term *somatopleure*. For the same reasons splanchnic mesoderm and entoderm together are designated as *splanchnopleure*.

The splitting of the lateral mesoderm does not occur simultaneously throughout its extent. The earliest indications of the process appear here and there in the more peripheral parts of the mesoderm. The first small local areas of separation give rise to isolated vesicles (Fig. 38, E) which rapidly extend and become confluent to establish the coelom (Fig. 38, F). A definite coelom is thus first established in the extra-embryonic portions of the mesoderm, and is correspondingly designated as the extra-embryonic part of the coelom, or, more briefly, exocoelom.

As development progresses, the splitting initiated peripherally continues to extend toward the embryo and soon involves the intra-embryonic portion of the mesoderm (Fig. 63, A, B). Thus, an intra-embryonic portion of the coelom is established which is at first directly continuous with the exocoelom (Fig. 71, A, B). Later in development, as the growing embryo is more definitely separated from its surrounding membranes, we see the demarcation between intra- and extra-embryonic coelom quite sharply established (Fig. 71, C). The part of the coelom then included within the embryo gives rise to its pericardial, pleural, and peritoneal cavities.

It is of interest to note that the first part of the intra-embryonic coelom to be established is the region where the heart will develop. The precocious formation of the pericardial coelom presages the early appearance of the cardiovascular system as a whole. Another condition of interest is the extensive growth of the extra-embryonic layers, which foreshadows an early differentiation of the membranes derived from them. The accelerated differentiation of the cardiovascular mechanism and the trophic membranes is a very striking feature of mammalian development, which would seem to be quite definitely correlated with the paucity of yolk in the mammalian ovum. In the absence of a readily available supply of stored food material, membranes capable of establishing metabolic interchange with the maternal circulation and a fetal circulation capable of transporting and distributing the food material absorbed through these membranes are both indispensable factors for the growth of the embryo.

Embryological Importance of Germ Layers Not having at our disposal human material showing some of the critical stages in germ-layer formation, we have been at some pains to trace the establishment of the germ layers in another mammalian form. In looking back over this phase of development, perhaps the most conspicuous thing, at first glance, is the multitude of cells formed from the single fertilized egg cell by repeated mitoses. Of more significance, however, is the fact that even during the early phases of rapid proliferation the cells thus formed do not remain as an unorganized mass. Almost at once they become definitely arranged as a hollow sphere which is called the blastocyst. At one pole of the blastocyst there is aggregated a group of cells known as the inner cell mass. Scarcely is this established when certain cells begin to emerge from it to line a smaller inner cavity, the *primitive gut* or *archenteron*. These cells we recognize as constituting the entoderm. Shortly, a third cell layer makes its appearance between the first two, called, appro-

proportionately enough, the mesoderm. That part of the original aggregation of cells which is left covering the outside of the embryo, and constituting the outermost layer of its enveloping membranes, is the ectoderm. These three cell layers are spoken of as the germ layers of the embryo.

The germ layers are of interest to the embryologist from several points of view. The simple organization of the embryo when it consists of first a single, then two, and finally three primary structural layers is reminiscent of ancestral adult conditions that occur in primitive groups of the invertebrate series. From the standpoint of probable ontogenetic recapitulations of remote phylogenetic history, several facts are quite suggestive. The nervous system of the vertebrate embryo arises from the ectoderm—the layer through which a primitive organism which has not as yet evolved a central nervous system is in touch with its environment. The lining of the vertebrate digestive tube is formed from the entoderm—the layer which, in very primitive forms, lines a gastro-cele-like enteric cavity. The vertebrate skeletal, muscular, and circulatory structures are derived almost entirely from the mesoderm—the layer which, in small, lowly organized forms, is relatively inconspicuous but which constitutes a progressively greater proportion of the total bulk of animals as they increase in size and complexity and consequently need more elaborate supporting and transporting systems.

Interesting as are the possibilities of interpreting the germ layers from the standpoint of their phylogenetic significance, our chief concern with them centers about the part they play in the development of the individual. The establishment of the germ layers is the first segregation of cell groups which are clearly distinct from one another by reason of their definite relations within the embryo. The fact that these relations are fundamentally the same in all vertebrate embryos speaks forcefully of the common ancestry and similar heritage of the various members of this great group of animals. It means, furthermore, that in these germ layers we have a common starting point in the fabrication of the variations which different classes of animals have built upon the common underlying plan of body structure characteristic of the vertebrate group as a whole.

The establishment of the germ layers marks also a transition from the period of development when mere increase in number of cells is the outstanding event, to one in which differentiation and specialization are dominating concomitants of growth. Differentiation is occurring within the germ layers even before we can see tangible evidences of it by any of our present microscopical methods. Within a layer that looks all alike to us, there are gradually being established localized groups of cells with different developmental potentialities. We have long known that such must be the case because we could see various special structures, one after another, take shape from a germ layer that gave no advance notice by any visible changes of what it was about to do. Recent experimental work is beginning to give us information as to how long such invisible differentiation precedes the visible morphological localization of a cell group which we readily recognize as the primordium of a definite organ.

For example, although the chick's optic vesicle does not appear as a definite primordium until after 30 hours of incubation, if a narrow transverse strip of the ectoderm of a 12-hour embryo is cut out from the regions either side of Hensen's node and grown by tissue-culture methods, it will in due time show specialized cellular elements of types which occur only in the eye. A strip taken from another region, although it appears similar, when grown in culture will show no cells characteristic of the eye but will show different specific specializations.

Experiments such as these indicate the surprisingly early stage at which there is, within the germ layers, invisible localization of cells with different developmental potentialities. As development progresses, these localized cell groups are bodily and visibly sorted out. In some cases their sorting out is accomplished by a folding off from the parent germ layer, in other cases by migration of individual cells which later become re-aggregated elsewhere. From primordial cell groups thus derived, the organs with which we are familiar in the adult gradually take shape. The story of the embryological origin of the various parts of the body is, therefore, the history of the growth, subdivision, and differentiation of the germ layers. A skeleton outline of these processes is given in Fig. 40. This chart at the present stage of our study will serve as a means of pointing out in a general way whether the early processes we have been dealing with are leading. As we follow the phenomena of development farther we shall find that each natural division of the subject centers more or less sharply about some particular branch of this genealogical tree of the germ layers.

Structure of Young Human Embryos With the foregoing outline of the origin of the germ layers in another mammalian type as a background, we are in a better position to interpret the conditions seen in man. For many years the youngest reasonably well-preserved human embryo available for study was the so-called "Miller ovum."² Recently, Hertig and Rock have recovered two very young human embryos, one (Figs. 41, 43) probably a little younger than the Miller embryo, and the other (Fig. 42) a little older. These embryos are so exceptionally well preserved and prepared, and the illustrations and the descriptions of them are so much better than anything else available, that our conception of the structure of young human embryos can well be based on them with little reference to the few other, less favorably preserved, specimens of comparable ages.

In the light of our present knowledge, a plausible summary of the times at which critical embryological events would have occurred in an embryo such as the younger Hertig-Rock specimen might run somewhat as follows. *Ovu-*

² Very young human embryos are so rarely secured and are of such special interest that the custom has arisen of designating them by the name of the person recovering them. Ordinarily, it is the same person who places their description on record in the literature. In the case of the Miller embryo, however, we are indebted to Streeter for the availability of an exceptionally careful description.

In both embryological and obstetrical literature the term "ovum" has been widely used to cover such very young embryos and their chorionic vesicles. There seems no good reason for continuing to follow precedent in such a loose and confusing usage.



FIG 41 Hertig Rock 11-day embryo (Carnegie Coll , 7699), photographed $\times 30$, to show its relations in the uterine mucosa (After Hertig and Rock, Carnegie Cont to Emb , Vol 29, 1941) Compare with Fig 43, which shows same specimen in higher magnification



FIG 42 Hertig-Rock 12-day embryo (Carnegie Coll , 7700) and a small area of the immediately surrounding mucosa, photographed $\times 60$ (After Hertig and Rock, Carnegie Cont to Emb , Vol 29, 1941)

lation probably took place some 13 days after the first day of the mother's last menstrual period (Fig 24). A fruitful coitus was nearly coincidental with ovulation, and within a few hours of coitus the actual meeting of the gametes in fertilization took place near the fimbriated end of the uterine tube. On its three- or four-day journey through the tube, the first half-dozen cleavage divisions (Fig 33) were carried out so the embryo was entering the morula stage (Fig 34, A) on its arrival in the uterus. In the five or six days it remained



FIG 43 Hertig-Rock 11-day embryo (Carnegie Coll., 7699) photographed $\times 150$ (After Hertig and Rock, *Carnegie Cont. to Emb.*, Vol 29, 1941) Compare with Fig 41, which shows same specimen in its relation to the uterine mucosa

free in the uterine cavity, the hollowing out of the morula to become a blastodermic vesicle occurred (Fig 34, C-E). About nine or ten days after its fertilization, and on the twenty-second or twenty-third day of the mother's menstrual cycle, the zona pellucida finally disintegrated, permitting the trophoblast to come in direct contact with and adhere to the uterine mucosa (Fig 80, A-C). It will be recalled that this would be the time when the uterine mucosa was entering on its phase of congestion and heightened secretory activity preceding the next expected period (Figs 23, 24). Immediately following its adherence, the rapidly growing trophoblast began to invade the

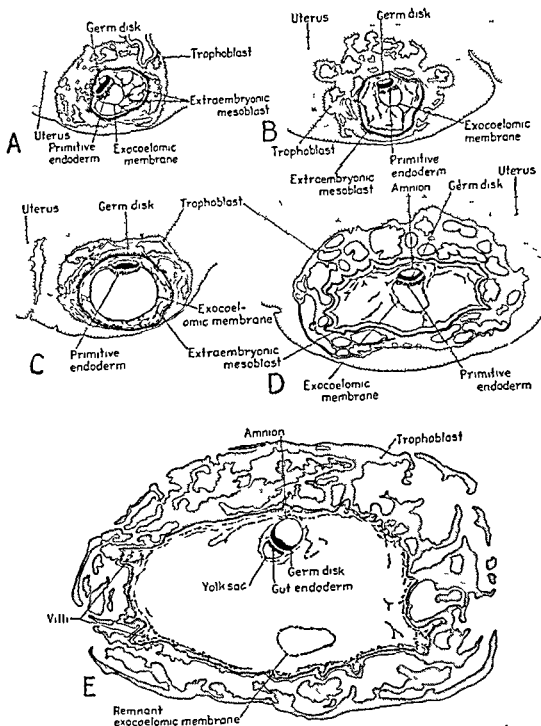


FIG 44 Outlines of five exceptionally well preserved young human embryos diagrammed to the same scale ($33\frac{1}{3}$) (After Hertug and Rock, Carnegie Cont to Emb, Vol 29, 1941)

- A, Carnegie embryo 7699 (Hertug-Rock), about 11 days
- B, Carnegie embryo 4900 (Miller-Streeter), about 11 days
- C, Carnegie embryo 7700 (Hertug-Rock), about 12 days
- D, Werner-Stieve embryo, about 12 to 13 days
- E, Edwards-Jones Brewer embryo, about 14 to 15 days

uterine mucosa (Figs 80, F, 81) In another day the growing villi had burrowed into the endometrium until the embryo became completely embedded (Figs 41, 82) It was at this time, probably about 11 days after fertilization, that the necessity of surgical removal of the uterus led to the recovery of this exceptionally interesting embryo (Fig 43)

In Fig 44, the two Hertig-Rock embryos have been diagrammed to scale in comparison with three other famous young embryos. It is quite evident that in even the youngest of this group differentiation of the germ layers is well under way. In the older specimens the entoderm has emerged from the inner cell mass and constitutes the lining of a primitive gut-yolk-sac cavity. This cavity has the same positional relations with reference to the remainder of the inner cell mass, and to the outer or trophoblast layer of the blastocyst as the newly formed primitive gut of the pig embryo (Cf Fig 36 with Fig 44.) The fact that the human yolk-sac is much smaller than that of the pig is neither particularly surprising nor significant. We may make a plausible guess that the entoderm cells lining the primitive gut in a human embryo first emerged from the inner cell mass in much the same manner as they have been seen to arise in pig embryos.

Comment has already been made on the leisurely manner in which the pig goes through many of the early phases of its development as compared with the hastening and slurring over of the corresponding processes in man. The formation of the mesoderm well exemplifies this contrast. In the young human embryos, although the entoderm appears to be scarcely established, the mesoderm extends well beyond the region of the embryonic disk. Its somatic component is already becoming applied to the trophoctoderm to form an extra-embryonic layer of somatopleure, and its splanchnic component is similarly associated with the entoderm of the primitive gut to form splanchnopleure (Fig 45). The extra-embryonic coelom thus confronts us abruptly as a capacious space, instead of our being able, as was possible in the pig, to watch it gradually form by the more and more marked splitting of an originally solid sheet of mesoderm. Moreover, the manner in which the extra-embryonic mesoderm in human embryos first makes its appearance suggests that it may arise, in part at least, by emergence of cells from the inner face of the trophoblast layer, as well as by proliferation from the inner cell mass. Nevertheless, as was the case with the entoderm, once the mesoderm is well established one finds it has the same fundamental relations in man that it has in those standbys of didactic embryology, the chick and the pig. Again we are tempted by the similarity of the end-results to guess that there might be in very young human embryos a proliferation center at a region corresponding to the posterior quadrant of the embryonic disk of the pig. But in keeping with the hastening of all these early processes in man any such center must be thought of as appearing relatively earlier, almost before there is sufficient differentiation of the embryonic disk to permit us to speak of its topography.

The peculiarity of very young human embryos in which they perhaps differ most strikingly from pig embryos is the early appearance of the amniotic cavity above the embryonic disk. When, in Chapter 6, the extra-embryonic membranes are discussed, we shall see how the amnion in more primitive forms arises relatively much later in development by the coalescence of folds of somatopleure. Discussion of the homologies of the amnion can best be postponed until they are taken up in that chapter. At present it is sufficient to note

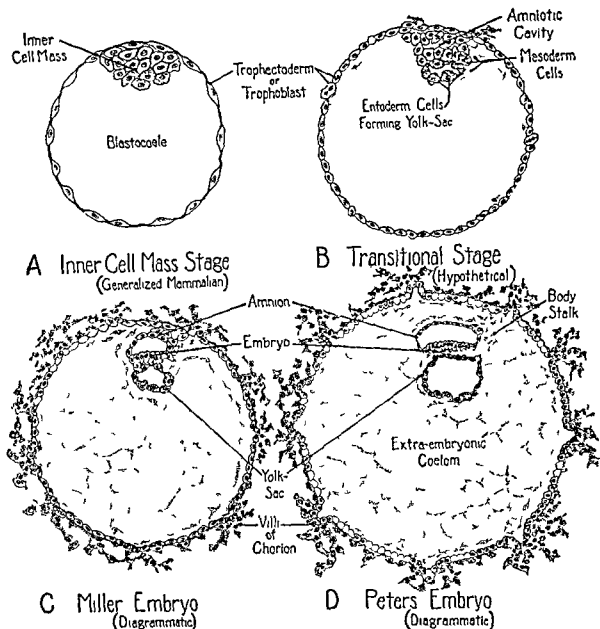


FIG 45 Schematic diagrams indicating the probable manner in which the structural plan exhibited by the youngest known human embryos is derived A, Generalized scheme of mammalian blastodermic vesicle There is no reason to believe that the human embryo, if secured about a week after fertilization, would show any essential differences from this plan which is common to all the higher mammals as yet critically studied (Cf Fig 35) B, Hypothetical transitional stage Probable condition of human embryo about eight or nine days after fertilization C, Schematized plan of the youngest well-preserved human embryos D, Schematization of the Peters' embryo, probable fertilization age of about 13 to 14 days The capacious extra-embryonic coelom is already completely lined by mesodermal cells (shown in red) and contains a granular material called the magma reticulare This "magma" is probably the result of the coagulation during fixation of a protein containing fluid which filled the exocoelom during life The scattered cells frequently seen in the magma may be regarded as migratory mesoderm cells which had not at the moment of fixation found their place in the exocoelomic lining

that the human amnion, like that of more primitive mammals, is composed of a layer of somatopleure, although it arises exceedingly early by what seems almost like a sleight-of-hand rearrangement of cells, rather than by the gradual folding process characteristic of such forms as the chick or the pig. Nevertheless, the layers composing it, and the final relations of the amnion to the body of the embryo and to the other extra-embryonic membranes in man, again run true to the fundamental pattern established by more primitive forms (Fig 78)

The Peters' embryo and the Warner-Stieve embryo which are perhaps two or three days older than the Hertig-Rock and the Miller embryos, have the same general structural plan, but the plan is sketched in sharper outline (Figs 44, D, 45, D), the embryonic disk being more clearly delimited and the amnion and yolk-sac easier to recognize. The most significant advances are in the separation of the amnion from the outer wall of the blastodermic vesicle and in the beginning of a definite body stalk. The body stalk at this stage is merely a mass of mesodermal cells attaching the embryo to the inside of the blastodermic vesicle. As is the case with so many things in early human development, it symbolizes a growth process which takes place relatively later in development, and is much more readily followed in lower forms. The body-stalk mesoderm stands for a precociously formed and somewhat atypical allantois. At this stage the chief clue to its homology is to be seen in the rudimentary allantoic lumen projecting into it for a short distance from the posterior part of the primitive gut (Figs 45, D, 70). Later we shall see its homologies more strikingly emphasized by the relations of the blood vessels which transverse it, placing the embryo in communication with the outer layers of the vesicle, and thereby establishing metabolic relations with the uterine circulation (Fig 78, C).

The formation of the body is of course initiated by the same growth processes which establish the germ layers. But even after the germ layers have been laid down and have begun to show considerable differentiation, the configuration of the young embryo is so unlike that of the adult that, except to one familiar with embryology, there are no readily identified landmarks. There is no distinct head, no neck, no trunk, there are no appendages—in short, there are none of the conspicuous structural features by which we are accustomed to orient ourselves in dealing with adult anatomy.

In the Miller or the Hertig embryos the embryonic disk, which is all there is in the way of a body, lies between the rudimentary yolk-sac and the amniotic cavity. It consists merely of a layer of a few ectodermal cells, a few entodermal cells, and the beginnings of a cluster of mesodermal cells (Figs 42, 43, 45, C).

In the Peters' embryo (Fig 45, D), the embryonic disk has become larger and more clearly defined, but still shows no definite landmarks. It is about two weeks after fertilization, when the primitive streak makes its appearance, that the longitudinal axis of the body is first clearly defined. One of the best preserved and most accurately described specimens of this age is the Heuser embryo. The dorsal aspect of the embryonic disk of the Heuser embryo, after

the amnion has been removed, shows a conspicuous primitive streak, terminating cephalically in a well-defined Hensen's node (Fig 46, A, B) Transverse sections (Fig 46, C, D) show an arrangement of the germ layers readily comparable with that seen in other young mammalian embryos The entoderm lining the primitive gut and the yolk-sac is easily distinguished The ectoderm has become much thickened in the region of the embryonic disk

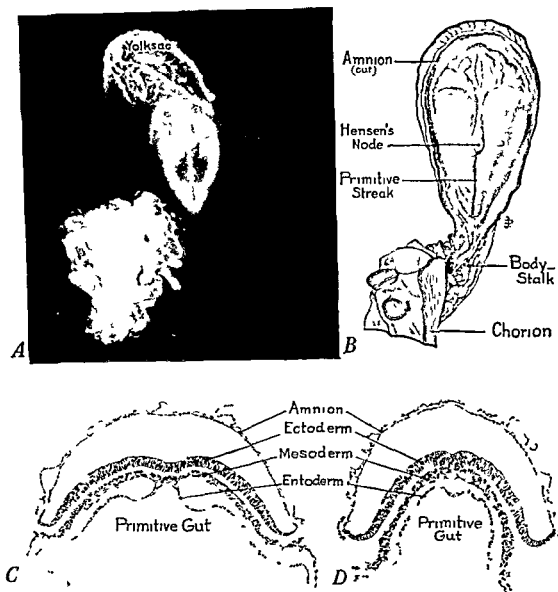


FIG 46 Human embryo in primitive streak stage—probable fertilization age of 14 to 15 days A, Photographed ($\times 18$) before sectioning B, Reconstructed from serial sections ($\times 25$) C, Section through neural plate D, Section through primitive streak (After Heuser, *Carnegie Cont to Emb*, Vol 23, 1932)

and shows a well-marked transition where it is continued extra-embryonically to line the amniotic cavity Within the body of the embryo the mesoderm is still a nearly solid sheet, but the presence of small vesicles already foreshadows its splitting into somatic and splanchnic layers Extra-embryonically the mesoderm is divided into a somatic layer most clearly seen where it turns dorsally to reinforce the amniotic ectoderm, and a splanchnic layer which turns ventrally to become associated with the entoderm of the yolk-sac

Thus, at the end of its first two weeks of development, we find the young human embryo with a body about 1.5 mm long, irregularly oval in shape, and with its long axis established by the primitive streak and the notochord. Internally, the three germ layers are clearly differentiated. It has been embedded in the uterine mucous membrane for perhaps four or five days, and the outer layer of the blastodermic vesicle in which it is contained has expanded in size and has firmly rooted itself in the surrounding maternal tissue. The foundations are now laid both for the further growth and specialization of its nourishing and protective membranes, and for the rapid development of the embryonic body.

Early Differentiation of the Body and Establishing of Organ Systems

EARLY DIFFERENTIATION OF THE BODY

Primitive Streak as a Growth Center In Chapter 4 we traced the formation of the primitive streak by the reshaping of a thickened, rapidly proliferating region in the posterior quadrant of the embryonic disk. We saw, also, the continued activity of the primitive streak in contributing cells to the rapidly expanding germ layers. This activity of the primitive streak as a growth center is an important factor in the formation of the early embryonic body.

Even casual inspection of a series of embryos of increasing age makes it apparent how rapidly the cephalic region is expanding (Figs. 46, 48, 49, 50). It is easy, however, to overlook the part played by the more caudal portions of the embryo in this cephalic growth. From the region of the primitive streak, cells are continuously being pushed forth into the growing body, but we see the results of the growth activities in the increase in size of other regions. Paradoxically, the primitive streak itself does not become larger by reason of its own activity, for the cells there proliferated promptly emigrate and the primitive streak itself becomes a relatively less and less conspicuous structure (Figs. 46, 48, 49). If an embryo in the primitive-streak stage has small areas marked by scarring with a hot needle and is then allowed to develop further, the peripheral expansion which takes place from the primitive streak can be vividly demonstrated (Fig. 47, D, E). One sees the expression of its growth activity in the rapidity with which the scars are carried peripherally. Particularly striking is the migration cephalad of scars made at the anterior part of the primitive streak.

The fact that the growth of a young embryo is taking place chiefly from its caudal end has a bearing, also, on the relative progress of differentiation in different regions of the body. It is a striking fact that the cephalic end of an embryo will always be found precocious in differentiation as compared with the more caudal portion of the body. This much-commented-on condition seems but natural when we consider that the head is actually older in development. For the structures behind the head are laid down by cells which were proliferated from the growth center at the primitive streak, subsequent to the establishment of the head itself. Of course differentiation does occur exceed-

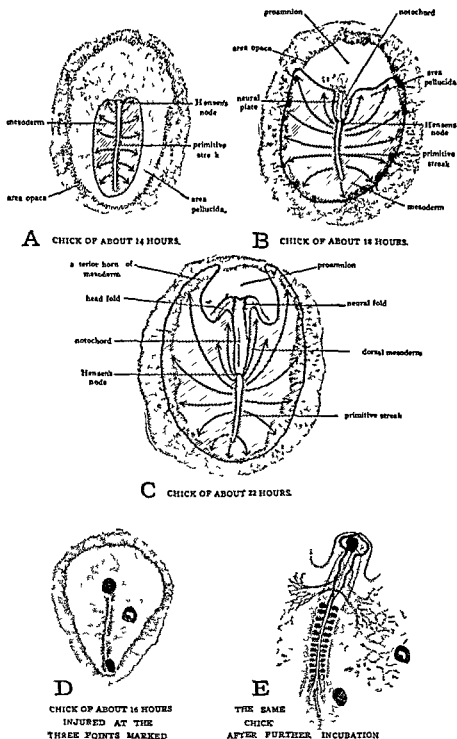


FIG 47 Diagrams, based on chick embryos, showing direction of growth from the primitive streak as a center A-C, Showing growth as expressed by the progress of the mesoderm during the latter part of the first day of incubation. Some of the more prominent structural features of the embryos are drawn in lightly for orientation but the ectoderm is supposed to be nearly transparent, allowing the mesoderm to show through. The area into which the mesoderm has grown is indicated by diagonal hatching. D, E, Showing direction of growth as demonstrated by experimental methods (After Kopsch). D, Showing location at which three injuries were made close to the primitive streak of a 16 hour embryo. E, Showing position to which injured areas were carried by growth of the same embryo subsequent to the operation.

ingly rapidly in the head. Were this not so other regions would pass it in developmental progress. But, in taking cognizance of this condition, we can not afford to overlook the fact that the head is given a considerable lead at the outset by its earlier establishment.

Early Differentiation of Cephalic Region From the standpoint of comparative anatomy and embryology, the developing head is divisible into a neurocranial portion and a visceral portion. The neurocranial portion includes—together with their supporting structures—the brain, the eyes, the internal ears, and the nervous part of the olfactory organs. The visceral portion includes the cephalic termination of the digestive-respiratory tract and the associated facial structures which are developed for the most part from

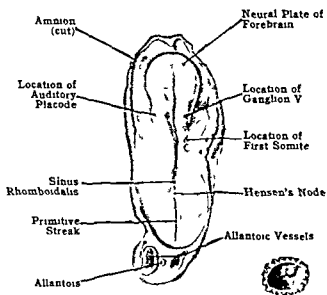


FIG. 48. A human embryo at the beginning of somite formation, $\times 30$ (After Ingalls, *Carnegie Cont. to Emb.*, Vol. 11, 1920.)

the primitive gill arch complex of water-living ancestral types. These two regions are unlike in their rates of growth and differentiation. The neurocranial portion is precocious, being very conspicuous in young embryos. Although its early predominance is never completely lost, it is greatly reduced in fetal and early postnatal life by the growth of the facial region which is relatively more rapid in these later phases of development.

In very young embryos the topography of the head is but vaguely defined. It soon, however, becomes more precisely marked out by the appearance of characteristic structures. Shortly after the primitive streak and the notochord have become clearly defined, the ectoderm in the mid-body region, cephalic to Hensen's node, becomes markedly thickened as compared with the rest of the superficial ectoderm. This thickening, known as the neural plate, almost immediately becomes folded into a longitudinal groove which heralds the formation of the central nervous system (Figs. 48, 49). With the establishment of the neural groove, landmarks begin to appear with rapidly increasing clearness. The neural folds in the anterior region are of much greater size than they

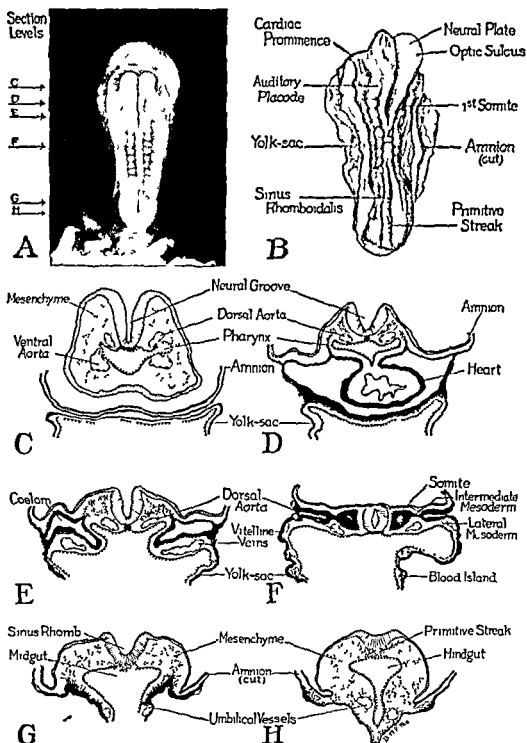


FIG. 49 Structure of human embryo in the seven- to eight-somite stage—probable fertilization age of 18 to 19 days A, Bartelmez eight-somite embryo (University of Chicago, H 1404), photographed ($\times 12\frac{1}{2}$) before sectioning B, Reconstruction of the Payne seven-somite embryo ($\times 22$) C-H, Sections of Bartelmez embryo at levels indicated in A, projection outlines ($\times 60$), schematically represented with ectoderm hatched, entoderm, a beaded line, mesenchyme, angular stippling, and the more solid parts of the mesoderm in black.

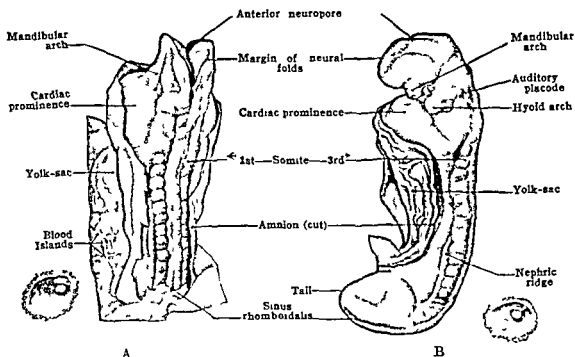


FIG 50 Two human embryos of about three weeks fertilization age A, Corner 10-somite embryo, probable age about 20 days, $\times 25$ (After Corner, Carnegie Cont to Emb, Vol 20, 1929) B, Heuser 14-somite embryo, probable age about 22 days, $\times 30$ (After Heuser, Carnegie Cont to Emb, Vol 22, 1930) Sketches in lower corners show actual size of respective embryos and their chorionic vesicles

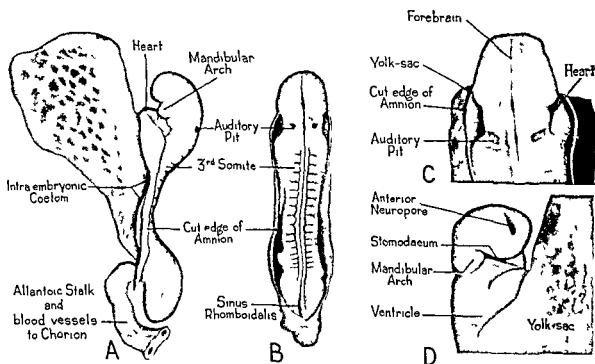


FIG 51 Four views of a human embryo of about three and a half weeks (Univ of Michigan Coll EH 195, 17 somites, cross-catalogued at the Carnegie Institution of Washington as 7702) Photographs retouched from the Carnegie stereophotographs A, Lateral view ($\times 16\frac{1}{2}$) B, Dorsal aspect ($\times 16\frac{1}{2}$) C, Dorsal view of head ($\times 27\frac{1}{2}$) D, Ventrolateral view of head ($\times 27\frac{1}{2}$)

are farther caudad. This condition foreshadows the differentiation of the neural tube into a conspicuously enlarged anterior portion, the brain, and a more attenuated posterior portion, the spinal cord. The cephalic region of an embryo of but three weeks' fertilization age is, therefore, already indicated by this anterior enlargement of the neural plate (Fig. 50).

Toward the end of the third or the beginning of the fourth week the primordia of both the ear and the eye become recognizable. The mechanism of the inner ears first appears in the form of a pair of thickened placodes in the

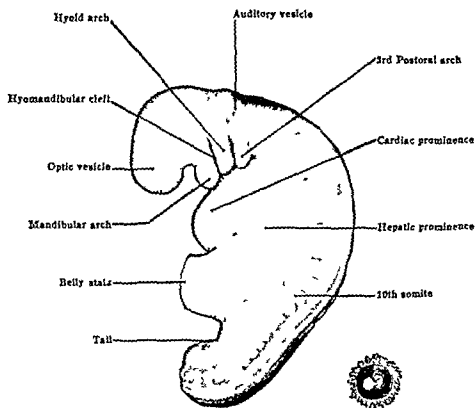


FIG. 52. Human embryo toward end of fourth week. Retouched photograph ($\times 20$) of embryo 6097 in the Carnegie collection, crown-rump length 3.6 mm, 25 pairs of somites. Sketch, lower right, shows actual size of embryo and its chorionic vesicle.

superficial ectoderm at the level of the more posterior part of the brain (Fig. 49, B). These primordial cell clusters soon sink below the surface to form the *auditory vesicles* (Fig. 239), and cease to be prominent externally (Fig. 52). Somewhat later, however, the beginnings of the external ear can be made out not far from the site of the original invagination of the internal ear primordium, and in close association with the hyomandibular cleft from which the Eustachian tube and middle-ear chamber are destined to be formed (Figs. 61, 62, 243, 244).

The eyes arise as local outgrowths from the lateral walls of the anterior part of the brain (Fig. 66). Long before the *optic vesicles*, as the early outgrowths are called, bear any resemblance to adult eyes, their position can be seen because of the prominence they make in the overlying ectoderm (Figs.

52, 53) Specializations of the superficial tissues about the optic vesicles soon make the developing eye readily identifiable (Figs 61, 62)

With the establishment of the brain, the ear, and the eye, there is no longer any difficulty in recognizing the general topography of the neurocranial part of the head. Meanwhile, the foundations of the visceral part of the head have been laid down. These primordial structures center about the *stomodaeal depression* which is destined to be molded into the mouth. Cephalic to the stomodaeum is the elevation caused by the overhanging forebrain (Fig 57). Cephalolaterally are the paired *maxillary processes* which are destined to form the lateral parts of the upper jaw (Fig 58). Phylogenetically, the maxillae are exceedingly ancient, being traceable to preoral arches in the invertebrate stock (probably primitive Arachnid types) from which the vertebrates were derived. At the bottom of the stomodaeal depression lies the *stomodaeal (oral) plate*. This is a thin, double-layered sheet of tissue—ectoderm outside and entoderm inside—which separates the stomodaeum from the originally blind end of the foregut (Fig 70, C). Late in the fourth week this membrane ruptures (Figs 56, 57, 70, D), establishing for the first time an oral opening into the foregut.

Caudal to the stomodaeal depression on the ventrolateral walls of the pharynx is a series of elevations with deep furrows between them (Fig 52). Although in mammalian embryos all these furrows do not break through into the pharynx, they are so clearly homologous with the similarly located clefts of fishes and amphibians that they are commonly called gill clefts. As the paired (right and left) elevations between adjacent clefts grow, they tend to merge with each other mid-ventrally in such a manner that each pair of elevations comes to constitute a sort of arch embracing the pharynx laterally and ventrally. The most anterior of the arches lies immediately caudal to the primitive mouth opening. Because it is involved in the formation of the lower jaw, it is called the *mandibular arch* (Figs 52, 57). Next behind the *mandibular* is the *hyoid arch*. The arches behind the hyoid, being unnamed, are referred to by numbers as postoral arches three, four, and five (rudimentary). As development progresses the arches posterior to the mandibular arch become less conspicuous and are incorporated into the neck (cf Figs 59–62), their deeper tissues giving rise to such characteristically located structures as the hyoid bones and the thyroid cartilages (Fig 106).

The first pharyngeal pouch—that is, the one internal to the groove between the mandibular and hyoid arches—is retained in part and becomes differentiated into the *middle-ear chamber* and the *Eustachian tube* (Fig 243). In embryos of about six weeks nodular masses of rapidly growing tissue appear about the external part of the hyomandibular cleft, initiating the formation of the external ear (Figs 61, 245). The more posterior clefts are, in the normal course of development, obliterated externally, but occasionally one of them may persist, giving rise to the anomaly known as a cervical fistula (Fig 330).

At about the stage of development when the visceral arches and clefts are most conspicuous, a pair of depressions appear at the rostral end of the head

These depressions, known as the *nasal pits* (Figs 58, 59) are surrounded by horseshoe-shaped elevations which gradually merge to form the nose (Fig 247) The details of this process will be considered later At the moment, it is sufficient to use the nasal pits along with the eyes and ears as landmarks in the developing head

Early Differentiation in Trunk Region Like their remote invertebrate forebears, all vertebrates have a segmentally organized body In adult mammals, the underlying metamerism is largely masked by local fusions and super-

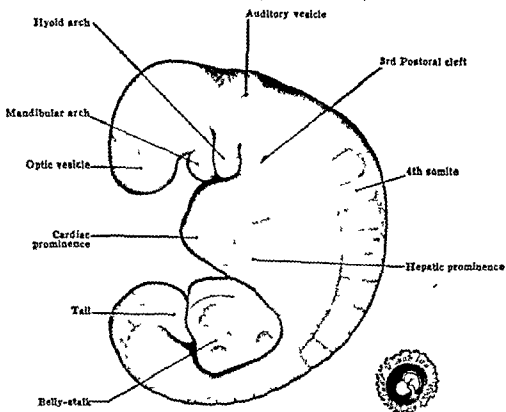


FIG 53 Human embryo about four weeks after fertilization Retouched photograph ($\times 20$) of embryo 5923 in the Carnegie collection, crown rump length 3.9 mm, 30 pairs of somites Sketch, lower right, shows actual size of embryo and its chorionic vesicle

imposed specializations But even so, unmistakable evidences of this fundamental plan of structure persist in the segmentally arranged spinal nerves and ganglia, in the vertebrae, and in the arrangement of the ribs and of the intercostal musculature In the young embryo, metamerism is much more obvious One of its most conspicuous superficial markings is the series of paired prominences which indicate the location of blocklike masses of mesoderm called somites (Figs 49-53) These aggregations of mesodermal tissue are clearly metameric in arrangement In fact, it is through them that we trace the origin of the segmental arrangement of the axial skeleton, the nerves, and the musculature just alluded to as one of the characteristic evidences of metamerism in adult anatomy (cf Figs 182, 183) These phases of the origin and relations of the somites will be returned to later For the present, it will suffice to note their metameric arrangement in the young embryo

The external prominence made by the developing heart appears at a strikingly early stage. The heart at first lies far toward the head as compared with its definitive position. Bearing in mind that the mandibular arch will form the lower jaw, we can say that the heart originates "under the chin" (Figs 50-52, 70). As growth proceeds, there is rapid elongation of the embryo between its head and trunk, which results in the establishment of the cervical region. In this process, the heart is carried caudad, to lie in its characteristic position in the thoracic part of the trunk (Figs 67, 68). It is in this change in

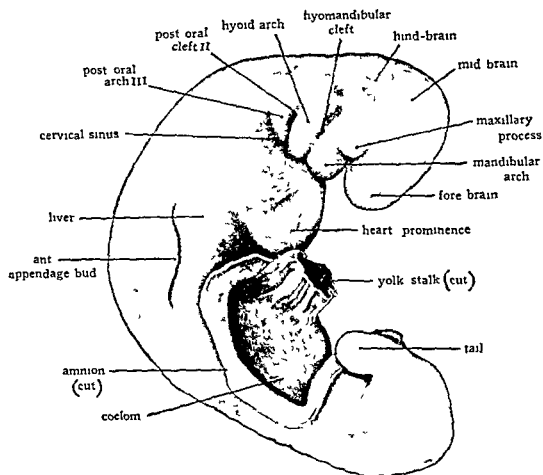


FIG 54 Photograph ($\times 18$) of a pig embryo of 5 mm. Compare with Figs 53 and 58 showing human embryos of closely comparable developmental stages.

the position of the heart that we find the key to the curious course of the associated vagus and sympathetic nerves. These nerves acquire their connection with the heart when it is still near the segmental level of their origin, and their fibers are pulled along with the heart in its migration caudad.

As early as the end of the fourth week, a slight depression may be seen between the cardiac prominence and the prominence due to the growing liver. This groove indicates the position at which the septum transversum, which is one of the primordial parts of the diaphragm, develops. With its appearance we can differentiate the thoracic from the abdominal region of the trunk (Figs 53, 58, 199).

Caudal to the hepatic prominence is the conspicuous belly-stalk (Figs 58,

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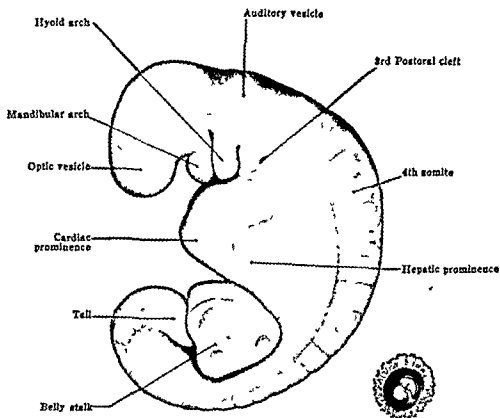


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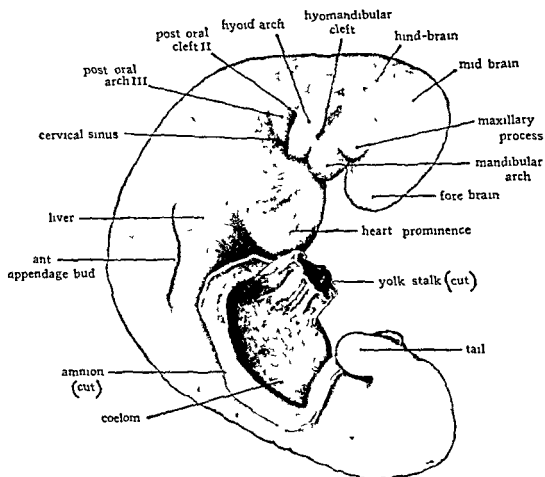


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EARLY DIFFERENTIATION OF THE BODY

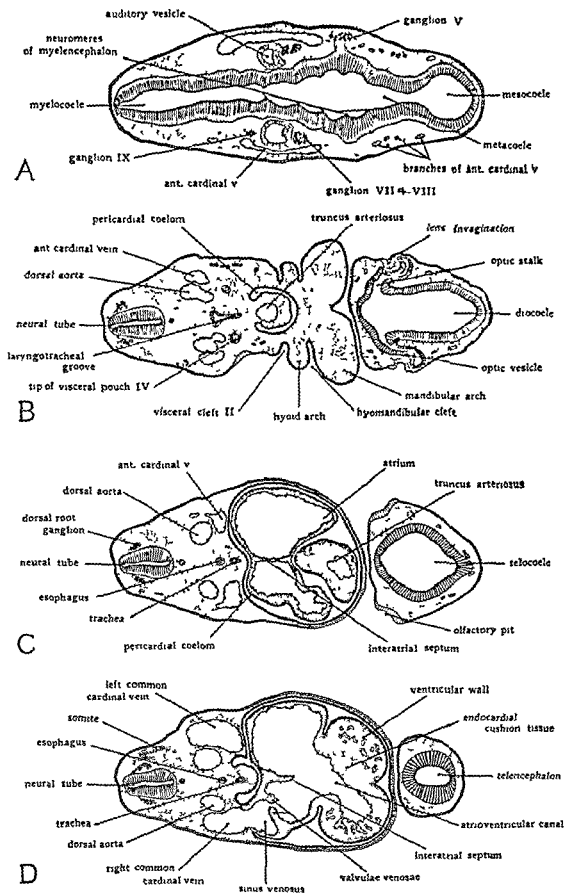


FIG 55 For legend and continuation of figure see facing page

59) Over this stalk, the tissues of the embryo are continuous with the extra-embryonic membranes, and in it are embedded the large blood vessels by way of which the embryo receives its food and oxygen supply from the uterus of the mother (Fig 78) Later, when the belly-stalk becomes much longer, and in relation to the size of the embryo much more slender, it is known as the umbilical cord (Fig 79)

During the fifth week of development, the appendage buds make their

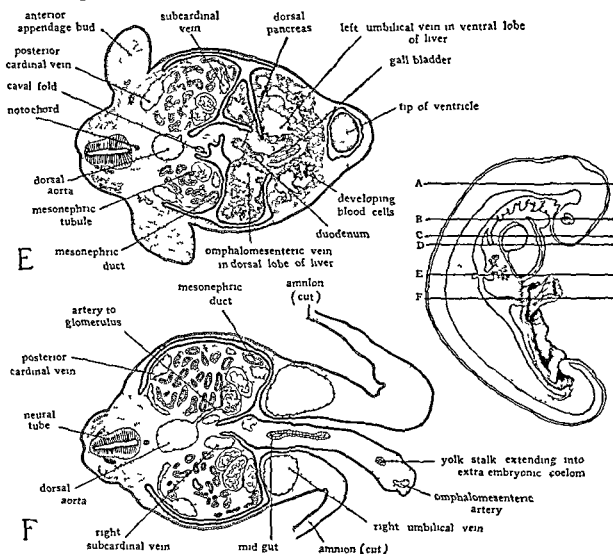


FIG 55 (Continued) Transverse sections of a 5 mm pig embryo (Projection diagrams, $\times 20$) Location of each section is indicated on the lateral plan of the body inserted opposite E and F

appearance The arm buds are formed adjacent to the position then occupied by the heart (Fig 58), at the metameric level of the fourth cervical to the first thoracic nerves It is in this location of their origin that we see the explanation of their characteristic innervation by the brachial plexus (Figs 182, 183, 199) The leg buds make their appearance about the same time, but their development lags a trifle behind that of the arm buds (Figs 58, 59) In their formation at the level of the lumbar and first sacral segments, the establishment of the sacral plexus is foreshadowed (Fig 199) The muscular tissue of the appendages is derived through budlike outgrowths from the mesodermic

somites at their metameric level (Figs 182, 185) Indications of the formation of digits first become apparent when the embryo has reached about the end of its sixth or the beginning of its seventh week of development (Figs 61, 62)

The embryos of all the higher vertebrates develop within a confined space

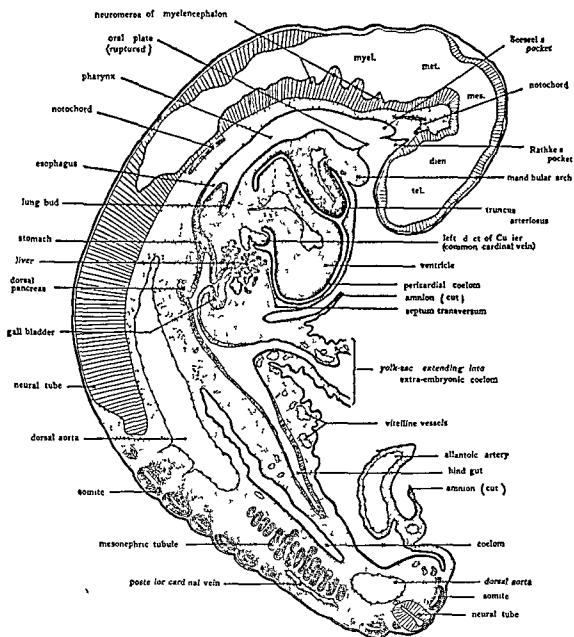


FIG 56 Longitudinal section of 5.5-mm pig embryo ($\times 25$) The caudal end of an embryo in this stage of development is usually somewhat twisted to one side For this reason sections which cut the cephalic region in the sagittal plane pass diagonally through posterior part of body

The growing body must conform itself to the limitations imposed by the egg shell, as in birds and reptiles, or the uterine cavity, as in mammals It is not at all surprising, therefore, that young embryos show a marked tendency to become curled, head to tail This process by which an embryo at first straight (Figs 48, 49, 50, A) becomes bent into more or less the shape of a letter C, is

called flexion¹ Flexion becomes apparent first in the cephalic region (Fig 50, B) but soon thereafter involves the entire body (Figs 52, 53) At certain points, the bending is especially strongly marked This has led to speaking—for convenience in description—of the cranial flexure, the cervical flexure, the dorsal flexure, and the lumbosacral flexure These so-called regional flexures in reality grade into one another and are nothing more than local accentuations of a curved configuration which involves the entire body

Early Differentiation of Mesoderm The mesoderm plays such an important rôle in the formation of so many parts of the body that its early differentiation demands special attention Its first appearance between the ectoderm and entoderm in the posterior quadrant of the embryonic disk, as well

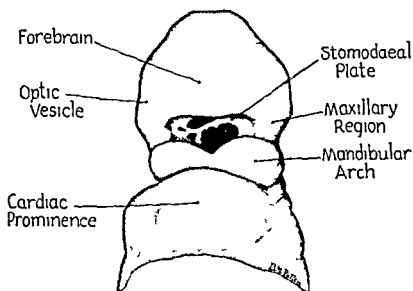


FIG 57 Breaking through of the stomodaeal plate to establish oral opening into foregut as seen in a face view of a human embryo of the fourth week (Drawn, $\times 30$, from stereophotographs of embryo 6097 in the Carnegie Collection) Compare with Fig 52, which is a lateral view of the same embryo

as its rapid spread from the primitive streak, has already been discussed (Figs 38, 47) As its differentiation is followed into older stages, it can be seen that the mesoderm on either side of the notochord becomes markedly thickened (Fig 63, A) These paired thickened zones from which the somites are formed constitute the so-called dorsal mesoderm Extending to either side from the zones of thickened dorsal mesoderm are the sheets of lateral mesoderm which start intra-embryonically and extend beyond the confines of the body as extra-embryonic mesoderm The splitting of the lateral mesoderm to form somatic and splanchnic layers bordering the coelom is already familiar from earlier stages

¹ It seems probable that the deeply concaved back depicted in many of the older illustrations of embryos in the transition phase from their early straight to their later convexly curved configuration is not normal This condition could well be due to uneven shrinkage in fixation or to traction exerted by the large yolk sac on the very slender body Even well preserved embryos, however, show a transitory concavity of their backs (Fig 51)

Between dorsal and lateral mesoderm is a narrow junctional zone known as the intermediate mesoderm (Fig 63, A, B) In the more cephalic parts of the body the intermediate mesoderm gives rise to the transitory urinary organs of early embryonic life, the pronephros and the mesonephros Its more caudal regions later become involved in the formation of the permanent kidney or metanephros

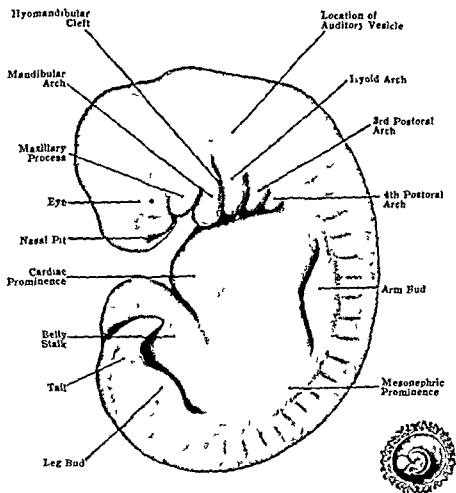


FIG 58 Human embryo early in the fifth week after fertilization (Crown-rump length 5 mm, drawing $\times 18$) Small sketch, lower right, shows actual size of embryo and its chorionic vesicle

It should be emphasized that the clear-cut differentiation of the mesoderm into the zones described above is characteristic only of the mid-body region (Fig 49, F) Both cephalically (Fig 49, C) and caudally (Fig 49, H), the mesoderm is represented at first by unorganized masses of sprawling, actively migrating cells designated collectively as mesenchyme

In human embryos, the first pair of somites appears about the sixteenth day after fertilization As continued growth from the primitive-streak region progressively increases the length of the embryo, the first somites formed are carried cephalad in the general expansion of the embryonic body Keeping

pace with the increase in cephalocaudal elongation, more and more dorsal mesoderm becomes differentiated posteriorly, and new pairs of somites are added behind those previously established. The increase in the number of somites in human embryos between the sixteenth day (when the first pair may be expected to appear) and the end of the fourth week (when ordinarily 30 pairs have been formed) averages between two and three pairs of somites a

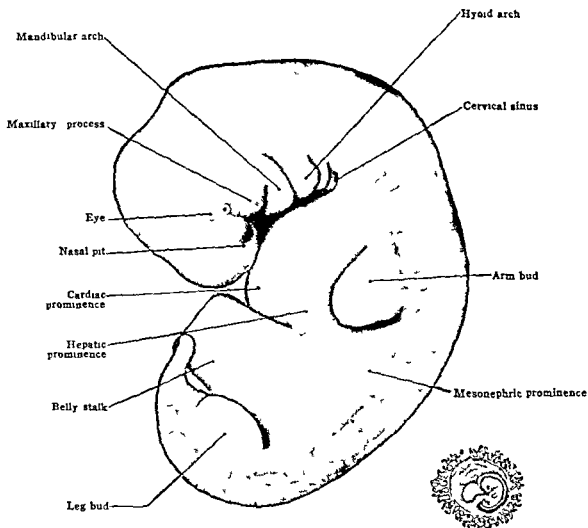


FIG. 59 Human embryo late in fifth week after fertilization (Crown-rump length 6.5 mm) Retouched photograph ($\times 15$) of embryo 6502 in the Carnegie Collection. Small sketch, lower right, shows actual size of embryo and its chorionic vesicle.

day. In other forms, where accurate age determinations are possible, the somites are known to be formed at a fairly steady rate. Although, as with all other growth processes, it is true that there is considerable individual variability and even litter-mates may have different numbers of somites, still, in very young embryos the somite count proves to be the most generally useful index of developmental progress. Especially in dealing with human embryos, which rarely come to the laboratory accompanied by anything like trustworthy data on fertilization age, the number of somites constitutes the best criterion of their relative stage of development.

The cells in a somite are not destined to a common fate—in fact, these cells as a group have a wider diversity of developmental potentialities than any sharply localized aggregation of cells in the young embryo. It is, therefore, a matter of special interest to see the various steps by which they become,

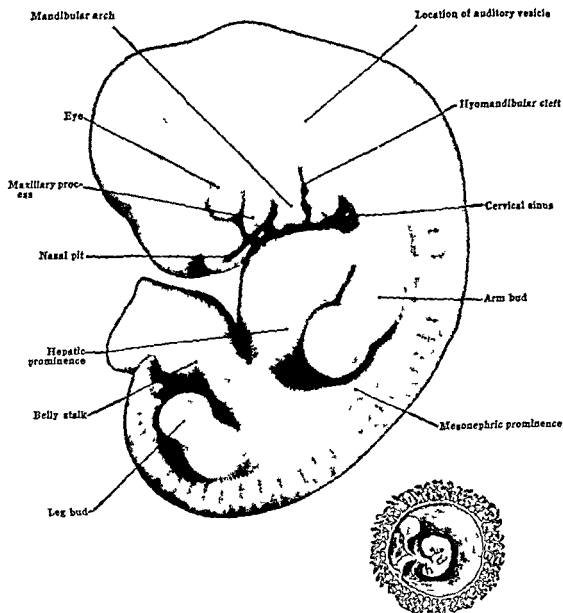


FIG. 60 Human embryo about middle of sixth week after fertilization (Crown-rump length 10 mm, drawing $\times 11$) Small sketch, lower right, shows actual size of embryo and its chorionic vesicle

so to speak, sorted out, grouped according to their potentialities, and finally highly specialized in various ways

The initial mass of cells constituting a somite grows rapidly in bulk, and the radial arrangement, at first vague, soon becomes clearly marked. At the same time, the boundaries of the somite become more definite and a small lumen appears in its center (Fig. 63, B). This lumen, known as the myocoel,

increases in size until the somite appears as a hollow vesicle with thick outer walls (Fig 63, C)

By this time, local differences within the somite are becoming apparent. Three regions are recognized and named on the basis of their later history. The dorsomesial part of a somite is composed of cells which will form the skeletal muscles developing at that segmental level of the body. For this reason it is called the myotome (Fig 63, D)

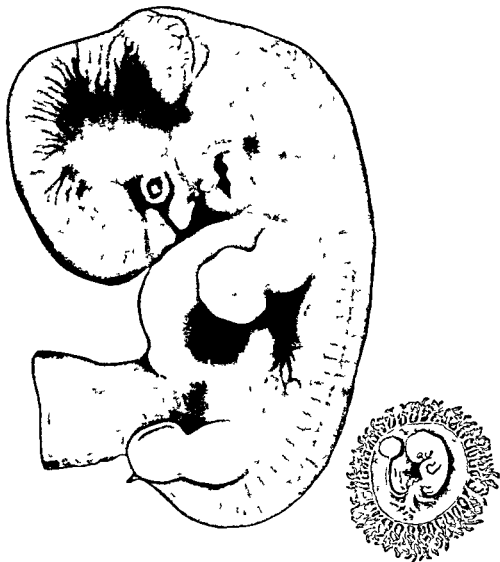


FIG 61 Human embryo a little over six weeks after fertilization (Crown-rump length 14 mm) Retouched photograph ($\times 8$) of embryo 1267A in the Carnegie Collection

The ventrolateral portion of the somite is made up of cells which have been believed to migrate out, aggregate close under the ectoderm, and give rise to the connective-tissue layers which underlie the epidermis. Accordingly, it has been called the dermatome or cutis plate. While some cells from this region of the somite undoubtedly are contributed to the formation of the deep layers of the skin, the conviction has been gaining ground that many, perhaps most of them, take part in the formation of muscle. Furthermore, the connective-tissue layer of the skin is known to receive many cells from the somatic meso-

derm generally, and from the diffuse mesenchyme in the cephalic region where there are no somites. The term dermatome is so firmly fixed that it is probably unwise to attempt to discard it, but we should bear in mind that, while it does contribute to the dermis, it probably does not do so any more extensively than other regions of the mesoderm which lie in close proximity to the ectoderm.

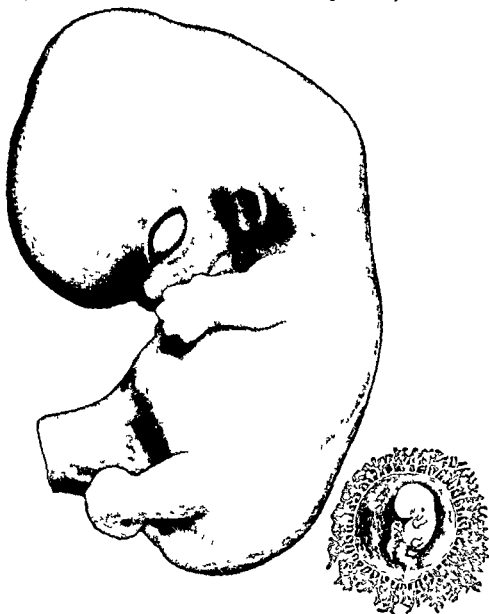


FIG. 62 Human embryo of about seven weeks fertilization age (Crown-rump length 17 mm.) Retouched photograph ($\times 7\frac{1}{2}$) of embryo 1324 in the Carnegie Collection.

The third region of the somite is the so-called sclerotome, consisting of cells which migrate ventromesially from the original compact mass (Fig. 63, C). These cells become concentrated about the neural tube and notochord, eventually giving rise to the vertebrae.

ESTABLISHING OF ORGAN SYSTEMS

In dealing with the development of the organ systems, two quite different methods of approach are possible. In one method, the structure of the embryo

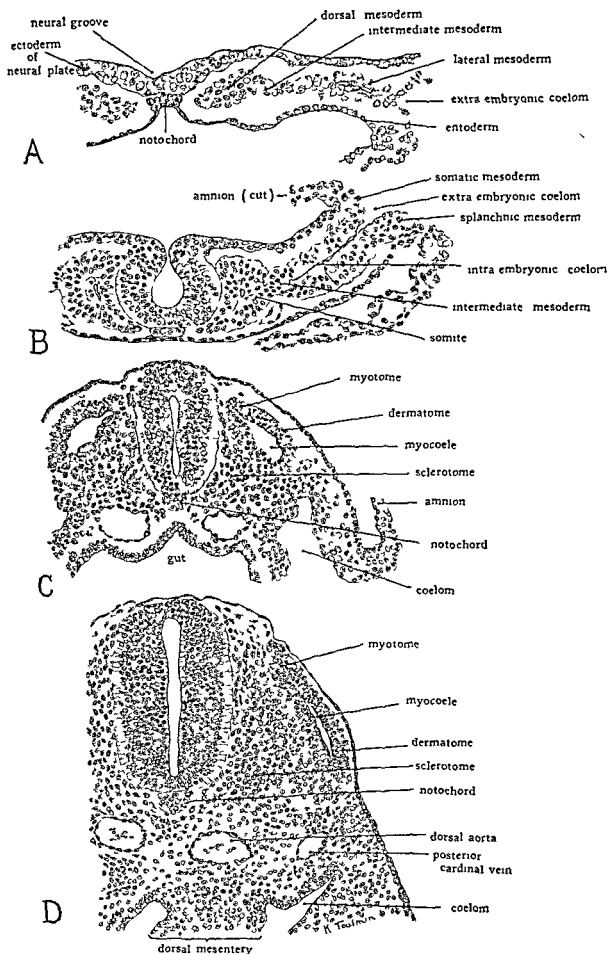


FIG 63 Drawings ($\times 150$) from transverse sections of pig embryos of various ages to show formation and early differentiation of somites (From series in the Carnegie Collection) A, Beginning of somite formation B, Seven somite embryo C Sixteen somite embryo D, Thirty somite embryo

derm generally, and from the diffuse mesenchyme in the cephalic region where there are no somites. The term dermatome is so firmly fixed that it is probably unwise to attempt to discard it, but we should bear in mind that, while it does contribute to the dermis, it probably does not do so any more extensively than other regions of the mesoderm which lie in close proximity to the ectoderm.

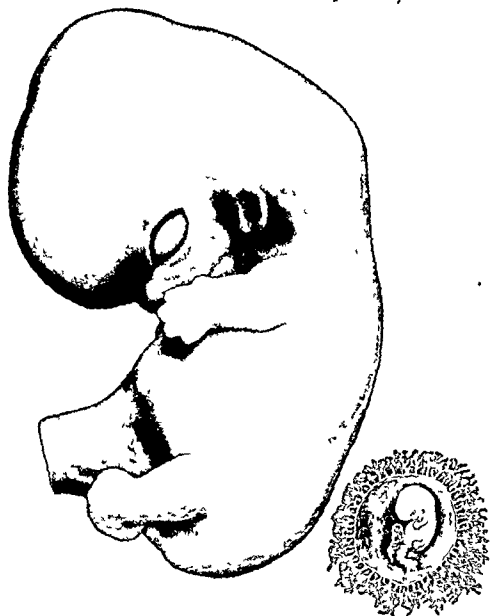


FIG. 62 Human embryo of about seven weeks fertilization age (Crown-rump length 17 mm.) Retouched photograph ($\times 7\frac{1}{2}$) of embryo 1324 in the Carnegie Collection.

The third region of the somite is the so-called sclerotome, consisting of cells which migrate ventromesially from the original compact mass (Fig. 63, C). These cells become concentrated about the neural tube and notochord, eventually giving rise to the vertebrae.

ESTABLISHING OF ORGAN SYSTEMS

In dealing with the development of the organ systems, two quite different methods of approach are possible. In one method, the structure of the embryo

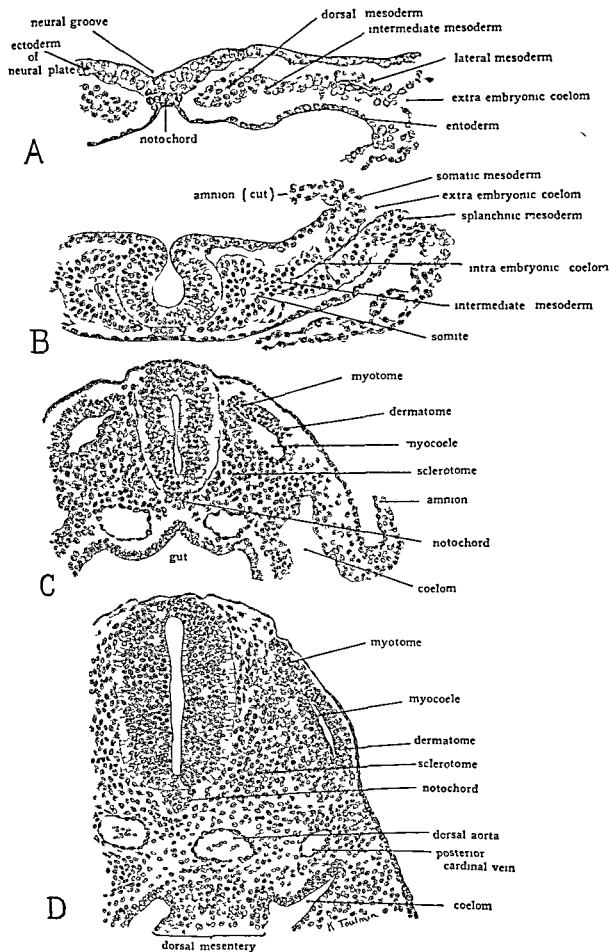


FIG 63 Drawings ($\times 150$) from transverse sections of pig embryos of various ages to show formation and early differentiation of somites (From series in the Carnegie Collection) A, Beginning of somite formation B, Seven-somite embryo C, Sixteen-somite embryo D, Thirty-somite embryo

including all its organ systems is considered at a succession of stages. This emphasizes the interrelations of the several systems, but forces one to cull material from many stages to fit together a coherent story of the development of any particular organ system. The other method is the separate tracing of each organ system from the appearance of its first primordia to its completed form. The advantage of this method lies in the sharper focusing of attention on *the changes involved in the formation of each particular system, and its weakness* lies in the loss of emphasis on the relations of one system to another in the embryonic body. The advantages of the method of presentation by stages are most marked in the early phases of development. While the organ systems are first taking shape they are themselves sufficiently simple in architecture so they can all be studied effectively together. Moreover, early in development such a procedure is especially desirable for the topography of the embryonic body, and the relations of one system to another are quite different from adult conditions and consequently need the greater emphasis.

As development progresses, conditions in each growing organ system become more complex, and we must pay increasing attention to the interrelations of the various parts developing within the system. At the same time, the general configuration of the body and the relations of one system to another are *rapidly approaching the more familiar conditions characteristic of the adult body*, so that they offer less difficulty. These considerations make the method of study by organ systems of greatest value in the relatively late stages of development. In planning this book, an attempt has been made to combine these two methods, using each for the phase of development to which it is best adapted. Accordingly, in this chapter we are trying to carry our study of all the organ systems along together until the embryo has reached an age of about six weeks. In subsequent chapters the story of the development of each organ system will be picked up separately and followed to its conclusion.

Such a plan of study has another advantage in that it facilitates the close correlation of the subject matter of the text with laboratory work. After an embryo begins to "look like a human being," students who are simultaneously studying embryology and adult anatomy have little difficulty in following developmental changes. It is when the body is first taking shape and the organ systems are barely sketched in unfamiliar lines that the study of embryology presents a special challenge to their intellect. It is for this reason that the major emphasis in the laboratory work in most embryology courses is laid on material such as pig embryos between 5 and 15 mm. in length. Such embryos are at the phases of development when the organ systems are first taking shape, and their study offers to the student an opportunity to acquire a grasp of basic embryological processes from his own laboratory study, such as no amount of purely didactic work can ever give.

Naturally, it would be preferable for medical students to study human embryos, but human embryos are not available in sufficient numbers for class use. The handicap, however, is not as serious as it might at first glance appear. At these early stages, before specific characteristics have begun to

emerge, the development of all mammals is closely parallel. In studying a 5-mm pig embryo, one is seeing an almost exact replica of the human embryo 4 weeks old (cf Figs 53, 54, 58). In working with a pig embryo of 10 mm, one is to all intents and purposes studying a human embryo of the sixth week (Fig 60). Thus the developmental processes of human embryos covered in this chapter readily can be illustrated in the laboratory with actual preparations of other readily available mammalian embryos such as pigs or rabbits. Conversely, the growth processes and the topographical relations here described for human embryos will apply equally well as a basis for interpreting the laboratory study of such forms.

NERVOUS SYSTEM

Formation of Neural Tube In dealing with the differentiation of the cephalic region, mention was made of a thickened area of the ectoderm called the neural plate (Fig 49). The first step in the formation of the central nervous

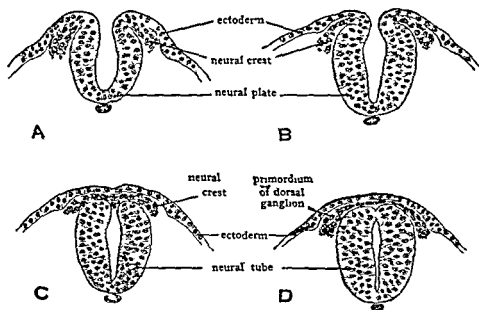


FIG 64 Drawing ($\times 135$) showing closure of neural tube and formation of neural crest. From pig embryos of A, 8 somites, B, 10 somites, C, 11 somites, D, 13 somites

system from this primordial mass of cells is its transformation from a superficial plate into a tubular structure lying beneath the rest of the ectoderm. As is the case with so many early embryological phenomena, this is brought about by a process which can be described most conveniently as folding. Due to differential growth, the neural plate becomes depressed centrally and elevated laterally, thus establishing the neural groove (Figs 49, C, D, 64, A). Continuation of this same process soon closes the groove into a tube. When the margins of the neural plate meet, a double fusion takes place. The mesial or neural plate components of the two folds fuse with each other, and the lateral limbs, consisting of unmodified ectoderm, also fuse with each other (Fig 64, B-D). Thus, in the same process, the original neural plate becomes the wall of the neural tube and the superficial ectoderm closes over the place formerly

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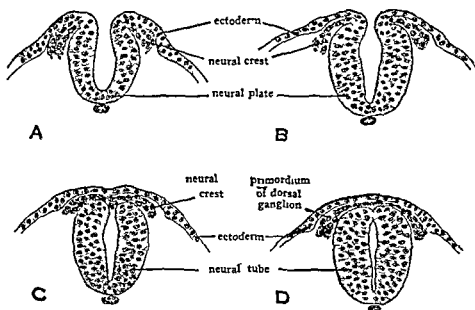


FIG 64 Drawing ($\times 135$) showing closure of neural tube and formation of neural crest. From pig embryos of A, 8 somites, B, 10 somites, C, 11 somites, D, 13 somites.

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ABBREVIATIONS FOR FIG 65

All St , allantoic stalk	N VI , sixth cranial (abducens) nerve
Br ep , eparterial bronchus	N VII , seventh cranial (facial) nerve
C I , dorsal root ganglion of first cervical nerve	N VIII , eighth cranial (acoustic) nerve
Ch t , chorda tympani branch of facial nerve	N IX , ninth cranial (glossopharyngeal) nerve
Dien , diencephalon	N X , tenth cranial (vagus) nerve
G acc , accessory ganglion	N XI , eleventh cranial (accessory) nerve
G acou , acoustic ganglion of eighth nerve	N XII , twelfth cranial (hypoglossal) nerve
G Trop , Tronsp's ganglion	N cerv d , descending cervical nerve
G gas , Gasserian (semilunar) ganglion of fifth nerve	N Ph , phrenic nerve
G gen , geniculate ganglion of seventh nerve	Na , location of nasal (olfactory) pit
G jug , jugular ganglion of tenth nerve	Nch , notochord
G nod , nodose ganglion of tenth nerve	Neur Cr , neural crest
G pet , petrosal ganglion of ninth nerve	Neph , nephrogenous tissue of metanephros
G pv , prevertebral sympathetic ganglion	Op c , optic cup
G sup , superior ganglion of ninth nerve	Oph V , ophthalmic branch of fifth (trigeminal) nerve
Gen Em , genital eminence	Ot , auditory vesicle (otocyst)
Gl B , gall-bladder	P C G , post-cloacal gut
Glom , glomerulus	P C V , posterior cardinal vein
L , lung	Panc d , dorsal pancreas
Lg Int , large intestine	Panc v , ventral pancreas
M Mes , Splanchnic mesoderm cut where reflected over mesonephros from mesentery	Pelvic Dil , pelvic dilation of metanephric diverticulum
Mand V , mandibular branch of fifth (trigeminal) nerve	Ph 4 , fourth pharyngeal pouch
Max V , maxillary branch of fifth (trigeminal) nerve	Rath p , Rathke's pocket
Mes , mesencephalon	Sm Int , small intestine
Mes D , mesonephric duct	St , stomach
Met , metencephalon	Sub Card Sin , large venous sinus formed by the transverse anastomosis of the subcardinal veins (subcardinal sinus)
Met D , metanephric diverticulum	Tr , trachea
Myel , myelencephalon	V T M , superficial mesonephric veins connecting post- and sub-cardinals (Named venae transversales mediales by Sabin)
N III , third cranial (oculomotor) nerve	
N IV , fourth cranial (trochlear) nerve	
N V , fifth cranial (trigeminal) nerve	

occupied by the open neural groove. Shortly after this fusion, the neural tube and the superficial ectoderm become somewhat separated from each other, leaving no trace of their former continuity.

Neural Crest There are cells located near the apices of the neural folds which are not involved in the fusion of either the superficial ectoderm or the neural plate. These cells form a pair of longitudinal aggregations extending, one on either side of the mid-line, in the angles between the superficial ectoderm and the neural tube (Fig 64, A, B). With the fusion which closes the neural tube, these two cell masses become, for a time, confluent in the mid-line (Fig 64, C). Because this aggregation of cells arises from paired primordia and soon again separates into right and left components, it should be thought of as a paired structure, although from its temporary medial position dorsal to the neural tube it was named the neural crest.

When first established, the neural crest is continuous anteroposteriorly. As development proceeds, its cells migrate ventrolaterally on either side of the spinal cord and at the same time become segmentally clustered. The metamerically arranged cell groups thus derived from the neural crest give rise to the dorsal root ganglia of the spinal nerves (Figs 65, 199), and in the cephalic region, to the ganglia of the cranial nerves which have sensory components (Fig 66).

Primary Brain Vesicles The marked enlargement of the anterior portion of the neural plate has already been commented on. When the neural tube is formed from the neural plate, the anterior part of the tube is of larger diameter corresponding to the greater size of the plate in the future brain region (Fig 49). The more slender portion of the neural tube caudal to the enlarged cerebral region is destined to become the spinal cord.

Almost from its first appearance, the brain shows certain indications of regional differentiation. In human embryos of the fourth week, three regions may be distinguished for the sake of convenience in description. These are the so-called forebrain, midbrain, and hindbrain (Fig 66, A). The forebrain (*prosencephalon*) is the broadest of the three because of the presence of the optic vesicles which arise as outgrowths from its lateral walls. In the extreme anterior portion of the forebrain, complete closure of the neural folds is somewhat delayed, and there remains, for a time, an opening known as the *anterior neuropore* (Figs 50, 51).

The midbrain (*mesencephalon*) is marked off by slight constrictions in the walls of the neural tube from the forebrain and, somewhat less distinctly, from the hindbrain (Fig 66, A). In young embryos, the mesencephalon shows little indication of local specialization presaging the formation of specific structures. Its roof is destined to become thickened and differentiated into the corpora quadrigemina (centers concerned with vision and hearing), and along its floor will develop the extensive fiber tracts of the *crura cerebri* which connect the more rostral parts of the brain with the spinal cord.

Posteriorly, the hindbrain, or *rhombencephalon*, grades without abrupt transition into the more slender part of the neural tube which will become the

spinal cord Its most interesting feature in early stages is the definite indication of neuromeric enlargements it shows, indicative of the fundamental metameric organization of the brain Concerning the precise homologies of individual enlargements in the brain of a mammalian embryo with specific neuromeres of ancestral forms, there is by no means complete agreement The controversies center about the fusion of neuromeres in the anterior part of the brain

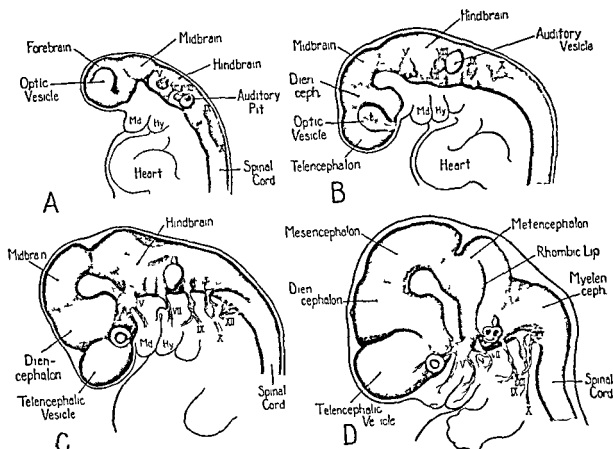


FIG. 66 Four stages in early development of brain and cranial nerves of young human embryos (Adapted from various sources, primarily figures by Streeter and reconstructions in the Carnegie Collection)

A, At 20 somites—based on the Davis embryo—probable fertilization age of three and a half weeks

B, At 4 mm, fertilization age of about four weeks

C, At 8 mm, fertilization age a little over five weeks

D, At 17 mm, fertilization age about seven weeks

The cranial nerves are indicated by the appropriate Roman numerals

V, Trigeminal, VII, facial, VIII, acoustic, IX, glossopharyngeal, X, vagus, XI, accessory, XII, hypoglossal Abbreviations Hy, hyoid arch, Md, mandibular arch

There are at least 11 enlargements recognizable in the embryonic brain, but only the more posterior ones show their individuality clearly Some of the more anterior enlargements undoubtedly represent several neuromeres In all probability, there are as many as 15 neuromeres represented in the vertebrate brain However this may be, for the beginning student the fact that metamorphism is unmistakably present is to be emphasized rather than the controversies concerning the homologies of neuromeres

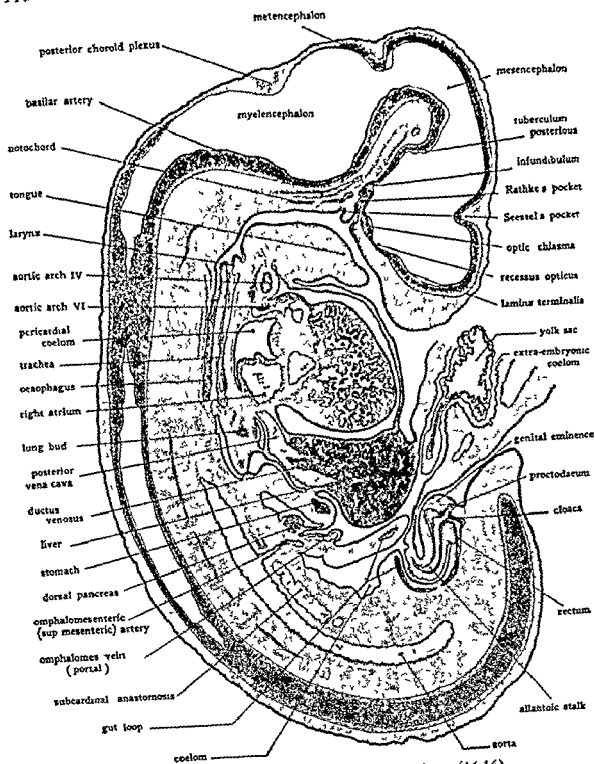


FIG 67 Sagittal section of 10-mm pig embryo ($\times 16$)

Five-vesicle Stage of the Brain The time during which the brain remains in the three-vesicle stage is brief. By the end of the fourth week there are indications of the impending subdivision of the prosencephalon, and soon thereafter a regional differentiation of the hindbrain also becomes apparent. By the sixth week of development, we can recognize five regional divisions in the brain. The prosencephalon has divided to form the telencephalon and diencephalon, the mesencephalon has remained undivided, and the rhombencephalon has become differentiated into metencephalon and myelencephalon (Figs 65, 66, 67).

The *telencephalon* consists of the most anterior median part of the brain, and two lateral outgrowths from it called the lateral telencephalic vesicles (Fig 66, C). Its posterior boundary is conventionally established by drawing a line from a fold in the roof of the brain called the velum transversum (see Fig 67, where the leader to Seessel's pocket crosses the dorsal wall of the neural tube) to the recessus opticus, a depression in the floor of the brain at the level of the optic stalks. Because this recess is just rostral to the optic chiasma, it is often called the *pre-optic* recess.

The *diencephalon* is the more posterior part of the old prosencephalon. Its posterior boundary is conventionally established by drawing a line from an elevation in the floor of the neural tube called the tuberculum posterius (Fig 67) to a depression in the roof of the neural tube which is just appearing at this stage of development, and may (Fig 68) or may not (Fig 67) be evident in the particular embryo under observation. The most conspicuous special features of the diencephalon are the paired lateral outgrowths from it which form the optic vesicles (Figs 65, 69, B) and the median ventral diverticulum which constitutes the infundibulum (Fig 67). The median dorsal outgrowth of the diencephalon known as the epiphysis, which is so conspicuous a feature in chick embryos of the third and fourth day, appears relatively late in the pig and in man. Ordinarily, no evidence of an epiphyseal evagination has appeared in human embryos of 9 to 11 mm, but suggestions of its formation can usually be made out in 12-mm embryos.

The *mesencephalon* shows little change from its condition in younger embryos. Its demarcation from the metencephalon posteriorly is indicated by a conspicuous constriction in the neural tube (Figs 65, 66, 67).

The division of the primitive hindbrain (rhombencephalon) into *metencephalon* and *myelencephalon* is indicated at this stage, though not conspicuous or definite. The dorsal wall of the neural tube just caudal to the meso-rhombencephalic constriction is markedly thick, contrasting strikingly with the very thin roof of the more posterior part of the hindbrain (Fig 67). The part of the neural tube where the dorsal thickening exists is the metencephalon, the posterior, thin-roofed portion of the hindbrain is the myelencephalon. Although all external indications of individual neuromeres have by this time disappeared, the internal face of the myelencephalic wall still shows definite neuromeric markings (Figs 68, 69, A).

Cranial Nerves The peripheral relations of the cranial nerves to cephalic structures and their central relations to the brain are strikingly constant throughout the vertebrate series. In fishes, we recognize 10 pairs of cranial nerves. In the mammals, we encounter these same 10 cranial nerves with

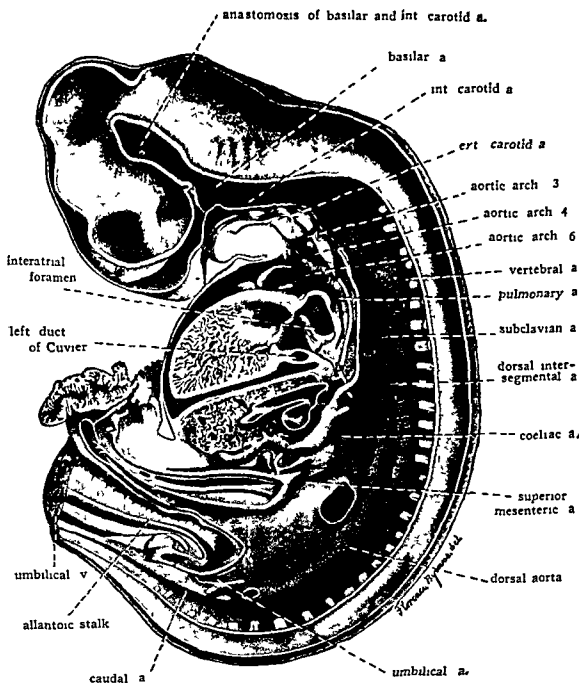


FIG 68 Reconstruction of 12-mm pig embryo showing relation of main arterial trunks to viscera (From Minot, after Lewis)

essentially similar relations both centrally and peripherally. But the mammalian brain, in its progressive specialization, has incorporated a part of the neural tube which in primitive fishes was unmodified spinal cord. One of the clearest evidences of this process is the fact that we find in the mammals 12

pairs of cranial nerves, the first 10 of which are homologous with the 10 cranial nerves of fishes and the last two of which represent a modification of nerves which in fishes were the most anterior of the spinal nerves

The 12 cranial nerves of mammals are designated by numerals almost as commonly as they are referred to by name Beginning with the most rostral they are (I) Olfactory, (II) optic, (III), oculomotor, (IV) trochlear, (V) trigeminal, (VI) abducens, (VII) facial, (VIII) acoustic, (IX) glossopharyngeal, (X) vagus, (XI) spinal accessory, and (XII) hypoglossal In six-week embryos, all of the cranial nerves except the olfactory and optic are readily recognizable (Figs 65, 66) Those carrying sensory (afferent) fibers show conspicuous ganglia near their point of connection with the brain (see nerves V, VII, VIII, IX, and X in Fig 66) Except for the acoustic (VIII), all these ganglionated nerves carry also some efferent fibers—that is, they are mixed nerves Those cranial nerves which are composed practically entirely of efferent fibers have no external ganglia (nerves III, IV, VI, and XII)

Spinal Cord and Spinal Nerves The posterior part of the myelencephalon merges without any definite line of demarcation into the spinal cord The walls of the neural tube in the cord region have already begun to become differentiated Dorsally and ventrally they remain thin, but laterally rapid proliferation of primordial nerve cells has caused them to increase greatly in thickness so that the originally oval lumen of the tube becomes slitlike (Fig 63, B-D) At the extreme posterior end of the developing spinal cord, closure of the neural folds is delayed, just as it was anteriorly The opening which thus persists for a time at the posterior end of the neural tube is known as the *sinus rhomboidalis* (Fig 50)

The cells arising from the neural crests (Fig 64) have become aggregated on either side of the cord into segmentally arranged clusters, the spinal ganglia (Figs 65, 199) From nerve cells in each of these ganglia, fibers grow both toward the cord and peripherally, establishing the dorsal roots (sensory root) of the spinal nerves (Figs 198, B, 200) The ventral (motor) root of a spinal nerve is composed of fibers which grow out from cells lying in the wall of the neural tube (Fig 198, B) Outside the cord, the dorsal and ventral roots unite to form the spinal nerve trunk

Immediately distal to the union of the dorsal and ventral roots of a spinal nerve, the nerve breaks up into three main branches (1) A dorsal ramus carrying the fibers associated with the dorsal part of the body, (2) a ventral ramus composed of fibers terminating in ventral parts of the body, and (3) a ramus communicans containing the fibers which extend by way of the prevertebral sympathetic chain to the viscera (Fig 200)

Primarily, the spinal nerves are strictly metameric in arrangement, each nerve carrying the sensory fibers from, and the motor fibers to, that segment of the body in which it arises But the underlying metamerism of the body in the adult is greatly modified—almost obliterated in many regions—by such processes as the fusion of primordial tissues from several metameres to form new, highly specialized structures, or by the migration of entire organs from

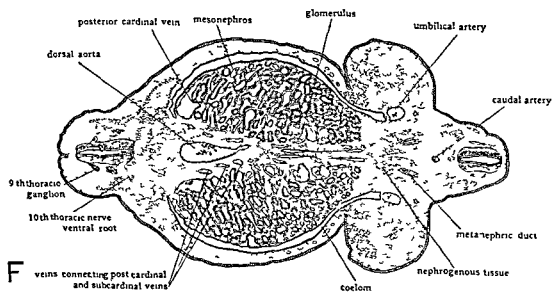
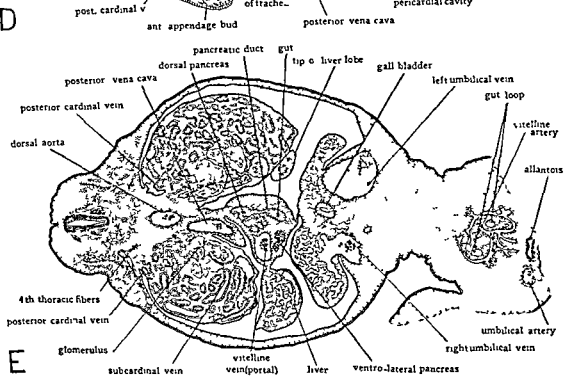
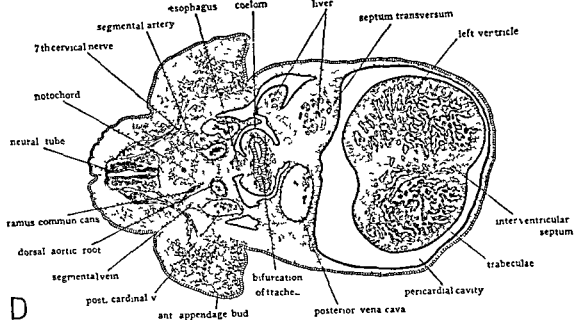


FIG 69 (Continued) Six cross-sections of a 94-mm pig embryo ($\times 18$)
 These sections are from the series used in making the reconstructions shown in
 Figs 65 and 75

D, Section No 309, through lung buds and liver

E, Section No 406, through pancreas and mesonephros

F, Section No 529, through metanephric primordia

their place of origin to new positions in the body. Since the spinal nerves arise very early in development and are at first associated with structures at their own metameric level, their final arrangement constitutes a valuable record of evolutionary and developmental history. The appendages, for example, arise by the coalescence and organization of primordial tissue from several adjacent metameres. The corresponding spinal nerves supply these tissues. Originally entirely separate, these nerves merge peripherally to form the nerves to the appendages. But the story of polymetameric development is permanently recorded by the series of nerve roots which retain their independent origin from the spinal cord in spite of their peripheral fusion in the brachial and sacral plexuses.

Furthermore, the caudal migration of the appendages during development is clearly evidenced by the fact that their nerves arise from the cord at a more cephalic level than that occupied by the appendages themselves. (Note the involvement of cervical nerves in the formation of the brachial plexus, as shown in Figs 65, 199.) Similarly, the caudal migration of the diaphragm from the place of its first appearance at what is destined to be the level of the neck is indicated by the cervical origin from the cord of the phrenic nerve to the diaphragm. In embryos of about 10 mm (Fig 199), the phrenic nerve can be seen extending almost directly from its level of origin toward the septum transversum which is the beginning of the diaphragm. Later in development, as the diaphragm moves caudad (Fig 304), the terminal portion of the phrenic nerve will be pulled caudad with it, constituting a permanent record of the migration of the diaphragm.

Sense Organs Although the sensory nerves associated with the nose and the eye are not noticeably developed in 10-mm embryos, the primordia of the sense organs themselves are established. The olfactory organs are represented by a pair of depressions situated at the rostral end of the head (Figs 58-60). From specialized cells in the ectodermal lining of these nasal pits, nerve fibers will later arise and grow into the telencephalon, establishing the olfactory nerves (Fig 229, D).

The single-walled spheroidal optic vesicle seen in younger embryos (Fig 66, A) has, by the sixth week, been converted by invagination of its distal portion into a double-walled cup (Fig 69, B). The inner layer of the optic cup is already much thickened, foreshadowing its development into the highly specialized sensory layer of the retina. The outer layer remains thinner and becomes the pigmented layer of the retina. The invagination of the primary optic vesicle to form the optic cup takes place eccentrically, and, as a result, the lip of the cup is not at first complete. It shows a ventral gap, called the choroid fissure (Fig 237, A), which does not close until later in development. (In Fig 65, the fissure is shown but not labeled, the section diagrammed in Fig 55, B, was cut somewhat on a slant so that the plane of the section passes through the choroid fissure in one eye but not the other.) The choroid fissure is continued as a groove on the ventral surface of the optic stalk. When the fibers which constitute the optic nerve grow from cells in the

sensory layer of the retina, they pass out of the optic cup by way of the choroid fissure and along this groove in the optic stalk toward the brain (Fig 234)

While these changes have been occurring in the optic vesicle, the lens has been established by invagination of the superficial ectoderm overlying the optic cup (Fig 55, B) By the time the embryo has attained a length of 10 mm, the lens has been completely separated from the parent ectoderm and appears as a spheroidal vesicle lying in the opening of the optic cup (Figs 65, 69, B, 231)

The primordium of the internal ear mechanism is as yet very simple in form It makes its first appearance as a local thickening of the superficial ectoderm overlying the hindbrain This thickened area then sinks in to form a pit, which soon becomes closed over to form the otic (auditory) vesicle (Fig 239) By the sixth week, the otic vesicle has entirely lost all connection with the ectoderm from which it was derived The only indication of its origin is a slender stalk, the endolymphatic duct, which extends dorsally toward the site of the original invagination (Fig 243, A)

Although the nerve connections of the auditory apparatus with the brain have not yet been definitely established, they are clearly indicated by the nerve fibers growing from cells in the acoustic ganglion toward the brain on the one hand, and toward the otic vesicle on the other Of significance, also, is the close proximity of the first pharyngeal (hyomandibular) pouch to the otic vesicle (Fig 65) This pouch is destined to give rise to the middle-ear chamber and the Eustachian tube (Fig 243)

DIGESTIVE SYSTEM

Delimitation of Intra-embryonic Gut Even before the body of the embryo takes shape, the formation of the digestive system has been initiated by the establishment of the entodermal layer within the spheroidal blastocyst (Fig 45) When the mesoderm has been formed and split into somatic and splanchnic layers, the splanchnic mesoderm becomes closely associated with the entoderm, the two layers together being known as the splanchnopleure Thus the primitive gut, very early in development, acquires a double-layered wall (Figs 46, C, D, and 49, E-G) The entodermal component of the splanchnopleure will give rise to the epithelial lining of the gut tract and to its glands The associated layer of splanchnic mesoderm becomes differentiated into the muscular and connective-tissue layers of the gut wall

By the time the wall of the primitive gut has received its mesodermal reinforcement, the embryonic body begins to be bounded by definite folds These body folds increase in depth and undercut the embryo, separating it, except for the communicating belly-stalk, from extra-embryonic structures At the same time they play an important part in determining the configuration and relations of the gut tract within the embryo This folding-off process begins with a ventral bending of the margins of the embryonic area so that the developing body takes on a marked dorsal convexity Then the undercutting

of these depressed margins cephalically and caudally, together with rapid increase in the length of the embryonic body, cause the embryo to overhang the extra-embryonic layers (Fig 70). Coincidentally the down-foldings on either side of the embryo become more definite, emphasizing its lateral boundaries (Fig 71, B). The progressive deepening of all these circumscribing folds and the continued growth of the body itself constricts the connection of the embryo with the extra-embryonic membranes, initiates the formation of the belly-stalk, and at the same time establishes the lateral and ventral body walls of the embryo (Figs 70, 71).

The superficial foldings which thus establish the boundaries between the embryonic body and extra-embryonic portions of the germ layers have their counterparts in the deeper lying layers. The changes which take place in the configuration of the splanchnopleure during this process bring about the division of the primitive gut into an intra-embryonic portion and an extra-embryonic portion known as the yolk-sac (Fig 71, A-C).

The first part of the primitive gut to be incorporated definitely within the body of the embryo is that portion lying beneath the head. With the forward growth of the head and its concomitant undercutting by the sub-cephalic fold, an entodermally lined pocket is established in the cephalic region. This is the foregut (Fig 70, B). Posteriorly, the foregut remains in open communication with the rest of the primitive-gut cavity by way of the anterior intestinal portal.

In a similar manner, a pocket known as the hindgut is formed beneath the caudal portion of the embryo. Anteriorly, the hindgut retains open communication with the rest of the primitive-gut cavity by way of the posterior intestinal portal (Fig 70, B).

Beneath the body of the embryo, between foregut and hindgut, is a region of the primitive gut which is destined to be included within the body, but which as yet has no floor. This region is known as the midgut. As the embryo is constricted off from the extra-embryonic layers by the progress of the sub-cephalic and subcaudal folds, the foregut and hindgut are increased in extent at the expense of the midgut. The midgut is finally diminished until it opens to the yolk-sac only by the restricted canal of the yolk-stalk (Fig 70, D).

Formation of Oral and Cloacal Openings When first separated from the yolk-sac, the embryonic gut ends blindly both cephalically and caudally, with no indications of either oral or cloacal openings. Soon, however, there appear two depressions in the surface of the body which sink in to meet the gut. One of these depressions, the *stomodaeum*, is located on the ventral surface of the head in the future oral region (Fig 70, C). The other, the *proctodaeum*, is located caudally in the future anal region (Fig 70, C).

The stomodaeal depression gradually becomes deeper until its floor makes contact with the entoderm of the foregut. The thin layer of tissue formed by the apposition of stomodaeal ectoderm to foregut entoderm is known as the *oral*, or *stomodaeal*, *plate*. As we saw in considering the early development of the head, it is not long after the first appearance of the stomodaeum that the

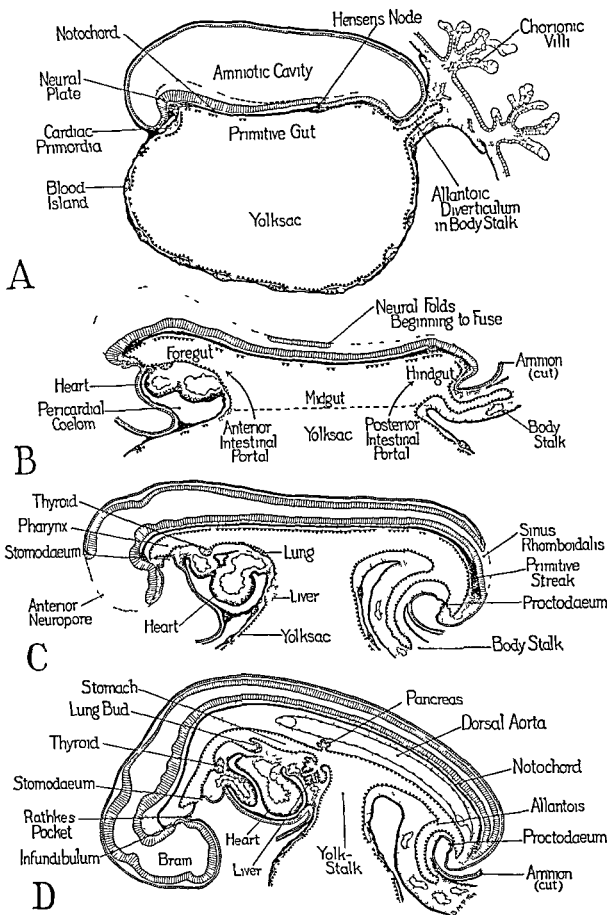


FIG 70 Sagittal plans of human embryos in third and fourth weeks to show establishment of digestive system. A, At the beginning of somite formation, age about 16 days (Based on Carnegie embryo 5080, and on the Ingalls embryo) B, Seven somites, age about 18 days (Based on the Payne embryo, see Fig 49, B) C, Fourteen somites, age about 22 days (Based on the Heuser embryo, see Fig 50, B) D, Toward end of first month (Based on Carnegie embryo 6097, see Figs 52, 57)

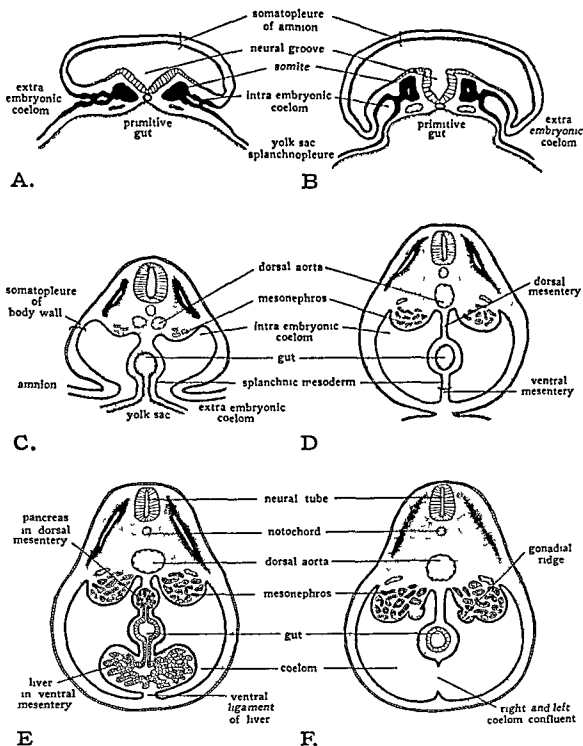


FIG 71 Schematic transverse sections showing closing off of embryonic gut from primitive gut, separation of intra- from extra embryonic coelom, and development of primary mesenteries

oral plate ruptures, establishing the cephalic opening of the gut (Figs 56, 57, 70, D)

A small diverticulum called *Seessel's pocket* persists as a vestige of the pre-oral gut which extended a short way cephalic to the point of rupture of the stomodaeal plate. Seessel's pocket is of no special interest in itself, for it gives rise to no adult structure. In embryos of this age, however, it is a valuable landmark, indicating as it does precisely the point at which stomodaeal ectoderm and foregut entoderm became continuous when the oral plate ruptured (Fig 56). Later growth of the surrounding structures further deepens the original stomodaeal depression, and it becomes the oral cavity. The region where the oral plate broke through in a four-week embryo becomes, in the adult, the region of transition from oral cavity to pharynx. Arising mid-dorsally from the stomodaeum is a narrow diverticulum known as *Rathke's pocket* (Fig 56). This ectodermally lined pouch grows toward the infundibular depression of the diencephalon, with which it will later fuse in the formation of the hypophysis.

Somewhat later in development than the time at which the oral opening is established, the proctodaeum breaks through to the hindgut, forming the cloacal opening. Subsequent differentiation in this region results in the separation of the originally single cloacal aperture into anal and urogenital openings.

Pharynx Caudal to the oral opening, the foregut becomes very broad and considerably flattened dorsoventrally to form the pharynx. A series of four pairs of pocketlike diverticula, the *pharyngeal pouches*, arise from it laterally. Each pharyngeal pouch is situated opposite one of the external gill furrows, the two together representing, as it were, an abortive attempt at establishing an open gill cleft. In mammalian embryos this process ordinarily stops just short of completion, the gill clefts remaining closed by a thin membrane. Arising medially in the floor of the pharynx, at about the level of the junction of the first and second gill arches, is an entodermal bud which is the *thyroid primordium* (Fig 70, D).

Trachea and Lung Buds In the floor of the pharynx, at the level of the most posterior pair of pharyngeal pouches, a median ventral groove appears which is rapidly converted into a tubular outgrowth parallel to the digestive tract. This groove is the tracheal (laryngotracheal) groove, and the tubular outgrowth which is formed by its prolongation caudad is the trachea. In six-week embryos the caudal end of the trachea has become enlarged and bifurcated to form the lung buds. Thus the original evagination from the pharynx is the primordium of larynx, trachea, bronchi, and lungs, but for the sake of brevity it is usually referred to as the "lung bud" (Figs 56, 70, C, D).

Esophagus and Stomach Caudal to the pharynx, the digestive tube is distinctly narrowed to form the esophagus. A marked local dilation, already of suggestive shape, indicates the beginning of the stomach (Fig 70, D).

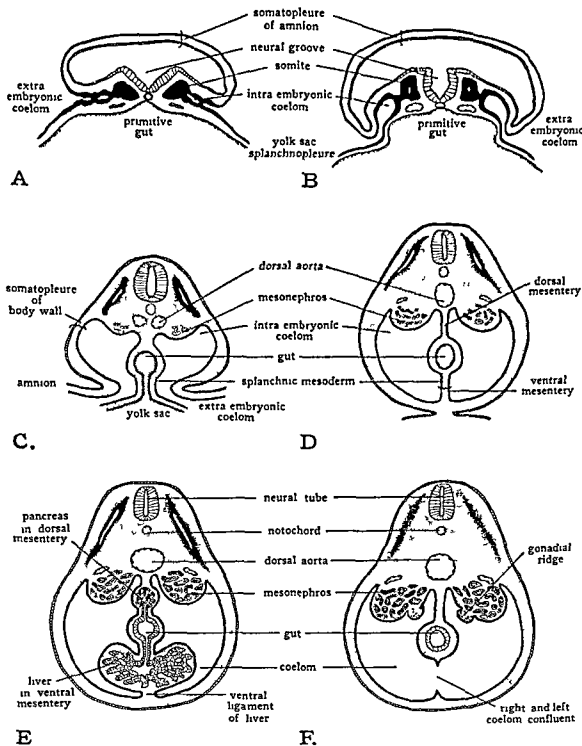


FIG 71 Schematic transverse sections showing closing off of embryonic gut from primitive gut, separation of intra- from extra embryonic coelom, and development of primary mesenteries

becomes the permanent kidney of the adult (Fig 337) We do not need to concern ourselves at the moment with either pronephros or metanephros The mesonephros, however, is such an important structure in embryos of this age, that, even though we are to consider it later in more detail, at this time we should at least note where it lies in the body and what sort of organ it is

The early stages in the formation of the mesonephros can best be seen in cross-sections of the embryonic body just posterior to the level of the heart The mesonephric ducts can be identified as cords of cells arising on either side of the body where somatic and splanchnic mesoderm merge into the intermediate mesoderm (Fig 338, C) Just mesial to the mesonephric duct, cells from the intermediate mesoderm become aggregated into a solid mass known as the nephrogenic cord When development has progressed somewhat farther, the nephrogenic cord can be seen to have given rise to a series of hollow vesicles, the primordial mesonephric tubules (Fig 56) These tubules soon make connection with the mesonephric duct, becoming at the same time much elongated and tortuous Meanwhile, the mesonephric duct becomes patent and establishes an outlet into the cloacal part of the hindgut

The origin of the mesonephroi from the intermediate mesoderm well localizes their initial position with reference to the coelom As they grow in mass, they bulge farther and farther into the dorsal part of the coelom (Fig 71, C-F) By the time an embryo has reached its sixth week, the mesonephroi form a pair of ovoid organs extending from the level of the heart to the extreme posterior portion of the body cavity Although they are similar in structure and position in the two species, the mesonephroi of young pig embryos (Fig 65) are relatively larger than those of human embryos of corresponding stages (Figs 353, 354)

A study of Fig 339 will make apparent the essential functional characteristics of the mesonephros It is made up of a mass of tubules, each having the relations to the vascular system and to the mesonephric duct there indicated schematically The glomerular tuft of capillaries pushing into the cup-shaped capsule at the distal end of the tubule, and the meshwork of capillaries surrounding the remainder of the tubule, provide a liberal surface exposure for vascular interchange The waste-containing fluids, drawn through the thin walls of the capillaries and through the epithelial wall of the tubule, are passed along the lumen of each tubule to be carried off by the mesonephric duct

COELOM

Very early in development, we saw that the lateral mesoderm became split into somatic and splanchnic layers with the coelom between (Figs 63, 71) As long as the somites and the intermediate mesoderm retain their early relations, the place of transition from somatic to splanchnic mesoderm is quite obvious and definite (Fig 63, B, 71, B) After the intermediate mesoderm becomes organized into nephric tubules and no longer connects the somite with the lateral mesoderm, the line of demarcation between splanchnic and

Liver and Pancreas Immediately caudal to the stomach are the outgrowths of the gut which constitute the primordia of the pancreas, and of the liver and gall-bladder. The pancreas arises as two independent parts, a conspicuous dorsal bud and a smaller ventral (ventrolateral) bud closely associated with the primordium of the liver (Fig 69, E). The original hepatic diverticulum (Fig 70, C, D) rapidly gives rise to a very extensive mass of glandular tissue which is crowded ventrally and cephalically from its point of origin to constitute the liver. The narrowed proximal portion of the original evagination from the gut persists as the duct draining the liver, and a diverticulum of it becomes enlarged to form the gall-bladder (Fig 287).

Intestines The elongation of the intestines which later results in their characteristic coiling has just commenced in six-week embryos. The gut has become relatively thinner than in earlier stages and protrudes into the belly-stalk in the form of a slender U-shaped loop (Figs 65, 273). Communicating with the gut at the apex of the loop is the yolk-stalk. The yolk-stalk by this time has become greatly attenuated and the yolk-sac with which it communicates is reduced to a shriveled vesicle embedded in the belly-stalk (Fig 67).

In some embryos in this age range a slight enlargement of the gut, just caudal to the point where the yolk-stalk connects with it, will suggest the beginning of the *cecum* (Fig 273). Cephalic to this enlargement the gut will become small intestine, and, caudal to it, large intestine.

The dilated caudal end of the gut where the allantoic stalk and the mesonephric ducts enter is called the *cloaca* (Fig 65). It is in this region that the proctodaeal depression ruptures into the gut, establishing its posterior opening to the outside. In an embryo of six weeks, the tissue intervening between the gut and the proctodaeum is never thick and may show signs of impending disintegration (Fig 67). Caudal to the level of the proctodaeum, a variable portion of the hindgut persists for a time as the so-called postcloacal (post-anal) gut (Fig 65).

UROGENITAL SYSTEM

As early as the fourth week of development, changes which foreshadow the formation of the embryonic excretory organs are becoming apparent in the intermediate mesoderm. By the sixth week, the mesonephros, which is a sort of temporary kidney, has become quite a conspicuous structure. But since the differentiation of other closely related parts of the urogenital system is as yet very slightly advanced, it seems advisable to postpone consideration of the system as a whole and to dismiss these early changes with a word of comment on the mesonephros.

The name *mesonephros* (middle kidney) implies the existence of a more anterior and a more posterior kidney. The anterior kidney (*pronephros*), while quite conspicuous in some of the primitive fishes, has entirely disappeared from the adult body of higher vertebrates and is vestigial in mammalian embryos. The posterior kidney (*metanephros*) appears later in development and

this stage, it is an ingrowth of ventral body-wall tissue fused to the cephalic face of the liver (Figs 301, 304) The septum transversum itself never extends all the way across the coelom Later in development, we shall see it supplemented by the pleuroperitoneal folds which arise from the dorsal body-wall, and complete the diaphragmatic partition across the coelom

CIRCULATORY SYSTEM

The mammalian embryo, having practically no yolk available as food, is dependent for its survival and growth on the prompt establishment of relations with the circulation of the mother This implies the necessity of a precocious development of the vascular system of the embryo, for the maternal circulation remains confined within the uterine walls and the embryonic circulation must grow to it Until this is accomplished the embryo is dependent on what food material it can obtain from the uterus by direct absorption—a method entirely inadequate to provide for the growth of the embryo except in its very early stages when its bulk is inconsiderable

Heart The heart of a human embryo begins to be formed during the third week of development from paired primordia situated ventrolaterally beneath the foregut The fact that the heart, a median unpaired structure in the adult, arises from paired primordia which at first lie widely separated on either side of the mid-line is correlated with the fact that the embryonic body at first is open ventrally and lies spread out prone on the surface of the yolk-sac The primordia of certain anatomically ventral structures arising at an early stage of development, therefore, first appear as separate halves lying on either side of the mid-line With the folding under of the lateral margins of the embryonic area, which brings the ventrolateral walls of the body into their definitive position, the embryo is closed ventrally and potentially midventral structures which arose as separate halves are established in the mid-line

The primordial heart is double-layered, as well as paired right and left The inner layer is called the endocardium because it is destined to form the internal lining of the heart The outer layer is known as the epimyocardium because it will give rise both to the muscular layer of the heart wall and to its epicardial investment

The endocardium appears first in the form of irregular clusters and cords of mesenchymal cells lying between the splanchnic mesoderm and the entoderm (Fig 72, A) These cells become organized into two main strands lying one on either side of the gut Soon after their establishment, the strands acquire a lumen and are known as the *endocardial tubes* (Fig 72, B) The endocardial tubes continue beyond the cardiac region as branching strands which will become, cephalically, the primitive aortas and, caudally, the *veins* entering the heart (Fig 73, A) The splanchnic mesoderm soon becomes markedly thickened where it is reflected laterally over the endocardial tubes to constitute the epimyocardial layer of the heart (Fig 72, B)

Meanwhile, folding off of the embryonic body is going on with concomi-

somatic layers is less readily determined. If, however, the position of the origin of the mesonephric tubules is taken as a landmark (Fig. 338, C), it becomes evident that the point at which somatic and splanchnic mesoderm become continuous may be located—with sufficient definiteness for all practical purposes—as the recess just lateral to the mesonephros (Fig. 71, C-F). This means that, because the mesonephros has been extended primarily ventromesially from its point of origin, it is the splanchnic mesoderm which is pushed out to cover the growing organ as it bulges into the coelom.

Similarly, in the cardiac region, somatic mesoderm ends at the angles of the coelom on either side of the pharynx (Fig. 49, D). The splanchnic mesoderm covers the ventrolateral walls of the pharynx, forms the dorsal mesocardium, and is reflected to form the outer covering of the heart wall. It is this characteristic relationship of the two layers which accounts for their names. The somatic mesoderm lines the body-wall (somatic) face of the coelom. The splanchnic mesoderm forms the supporting membranes (denoted by the prefix *mes*—e.g., mesocardium, mesogaster) of organs suspended in the coelom and covers the visceral (splanchnic) surfaces which project into the coelom.

With the folding off of the body from the extra-embryonic membranes and the closure of the embryonic body ventrally, the primary right and left coelomic chambers approach each other in the mid-line (Fig. 71, B-D). In this process, the gut tract is caught between the layers of splanchnic mesoderm which form the mesial boundaries of the coelomic chambers. The double layer of splanchnic mesoderm thus formed serves as a supporting membrane for the gut and is known as the mesentery. Shortly after its formation, the part of the mesentery ventral to the gut breaks through, bringing the right and left coelomic chambers into confluence and thus establishing a single body cavity within the embryo (Fig. 71, F).

Only in the mid-body region do these changes take place exactly as described above. While they are essentially similar elsewhere, there are certain local modifications of the process which are of special interest. At the level of the pancreas and liver, the ventral mesentery persists supporting these glands (Fig. 71, E). Where the extra-embryonic membranes are continuous with the embryo at the belly-stalk, the body cavity remains for a long time continuous with the extra-embryonic coelom (Figs. 67, 71, C). In the cardiac region, the digestive tract develops in the dorsal body-wall so that no dorsal mesentery is formed. Here the heart is formed ventral to the gut and suspended in the coelom by a double layer of splanchnic mesoderm in a manner somewhat suggestive of that in which the liver is suspended in the ventral mesentery farther caudally in the body (cf. Figs. 71, E, and 72, D).

In embryos of the ages under consideration, the body cavity is not yet divided into separate pericardial, pleural, and peritoneal chambers. Between the liver and the heart, however, there has appeared a shelf-like structure which partially separates the thoracic region of the coelom from the abdominal. This incomplete partition is called the septum transversum. At

ically where the ventral aortic roots branch out into the tissue beneath the foregut, and caudally where the great veins enter (Fig 300) Being unattached in its mid-portion, it is free to change its shape and position, and, since it grows much more rapidly in length than does the pericardial part of the

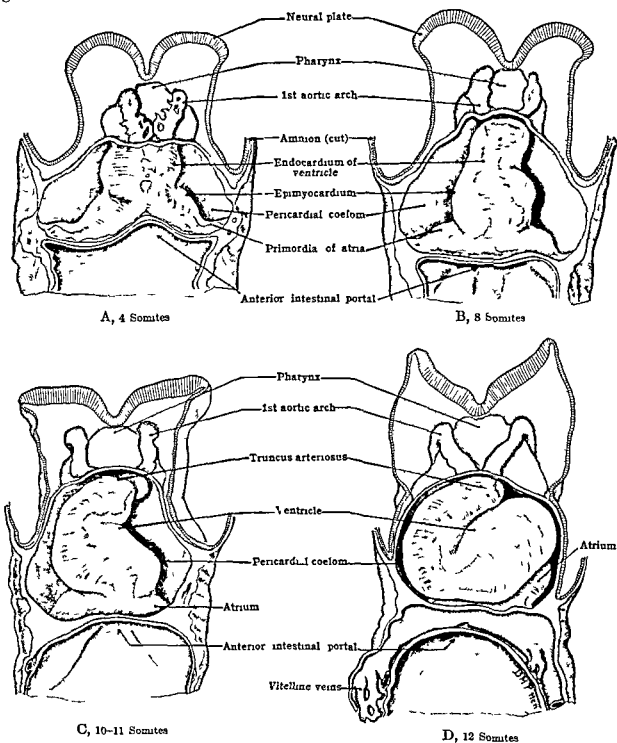


FIG 73 Four stages in formation of heart exposed by ventral dissection (Combined from the figures of Davis, Carnegie Cont to Emb, Vol 19, 1927)

coelom in which it is situated, the originally straight heart tube soon becomes conspicuously bent (Fig 73, C, D)

With the elongation and bending of the cardiac tube, its primary regional divisions begin to be recognizable. Naming them in the order they are

tant progress in the closure of the foregut at the level of the heart. As a result, the paired endocardial tubes are brought progressively closer together. Finally, they are approximated to each other and fuse to form a single tube lying in the mid-line (Figs 72, C, D, 73, B). In the same process, the *epimyocardial layers* are bent mesially, completely enwrapping the *endocardium*. Ventral to the heart, the mesodermal layers of the opposite sides of the body become continuous with each other so that, in the same process which estab-

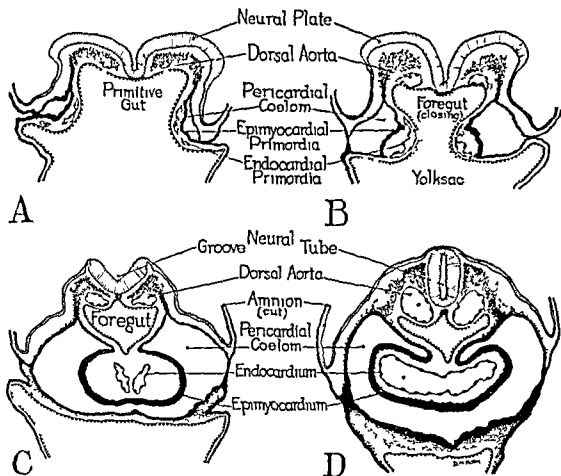


FIG 72 Four stages in fusion of paired primordia of heart as seen in cross-section A, Based on the Ludwig, two-somite embryo B, Based on the Carnegie 3709, four somite embryo C, Based on the Payne, seven somite embryo D, Based on the Corner, ten-somite embryo

lishes the heart as a median structure, the originally paired right and left *coelomic chambers* become confluent to form a median *pericardial cavity* (Fig 72, C, D). Dorsally, the right and left *epimyocardial layers* become contiguous, but here they do not fuse immediately, as happens ventral to the heart. They persist for a time as a double-layered supporting membrane called the *dorsal mesocardium*. In this manner, the heart is established as a nearly straight, double-walled tube suspended mesially in the most anterior part of the coelom.

The dorsal mesocardium soon disappears except at its caudal end so that the *tubular heart* comes to lie in the *pericardial cavity*, attached only cephal-

of functioning The heart tube has become bent and shows local dilations and constrictions which we are able to name because we know their future fate Many internal conditions point toward its division into right and left sides But the blood at this stage of development enters the heart posteriorly by way of the sinus venosus, is collected in the atrium, and passes into the ventricle whence it is pumped out by way of the truncus arteriosus as an undivided stream, just as was the case in younger embryos where the heart was still a relatively straight tube The partitioning of the heart into the four-chambered condition characteristic of the adult, which is only suggested at these early stages of development, is discussed in Chapter 19

Arteries While these changes have been occurring in the cardiac region, the main vascular channels characteristic of young embryos are making their appearance The cephalic prolongations of the endocardial tubes beyond the cardiac region constitute the start of the main efferent channels or aortae The aortae are further extended by a process similar to that involved in the formation of the endocardial tubes themselves Cords and knots of cells of mesodermal origin become aggregated along the course of the developing vessel These strands of cells are then hollowed out to form tubes, walled by a single layer of endothelial cells Where main blood vessels are about to become established there is found first a meshwork of these small channels Gradually, some of these primitive channels are enlarged and straightened to form the main vessels and their walls are later reinforced by the addition of circularly disposed connective-tissue fibers and smooth muscle cells In this manner, the primitive efferent channels are prolonged from the heart cephalad beneath the pharynx as the ventral aortae They then bend laterally and dorsally about the pharyngeal walls to form aortic arches, and finally turn caudad to extend nearly the entire length of the embryo as the dorsal aortae (Fig 74)

At first, there is but a single pair of *aortic arches* which is located in the tissue of the mandibular arch Later in their development, vertebrate embryos in general tend to form five additional pairs of arches connecting the ventral and dorsal aortae Each of these aortic arches lies in one of the visceral arches caudal to the mandibular The entire series of aortic arches, however, is never present at the same time in mammalian embryos, for the first two arches degenerate before the more caudal ones are formed, and the fifth is rudimentary and often wanting altogether From the functional standpoint, the significant thing is that blood passes by way of one or more pairs of aortic arches around the pharynx from the ventrally located heart to the dorsally located aortae which are the main distributing trunks of the embryonic circulation In human embryos of one month, the first three aortic arches are well formed and the fourth is usually just making its appearance (Fig 74) By the time the embryo has reached a size of 10-12 mm—that is to say, six weeks of age—the first and second arches have degenerated and the aortic arches present are the third, fourth, and sixth of the series (Figs 392, 393)

Throughout the length of the aorta, small branches appear at regular intervals and extend dorsad on either side of the neural tube Since these

traversed by the circulating blood, these regions are the sinus venosus, the atrium, the ventricle, and the truncus arteriosus. The *sinus venosus* is a thin-walled chamber formed by the confluence of the great veins entering the heart (Fig 417). Since the fusion of the cardiac primordia begins at their cephalic ends and progresses caudad, the sinus venosus is the last part of the heart to be established and at early stages shows but slight differentiation.

From the sinus venosus the blood passes into the atrium. Guarding the slitlike orifice between these two chambers against the return flow of blood are well-developed flaps known as the *valvulae venosae* (Figs 418, and 422, B-D). The *atrial region*, soon after it is established, undergoes extensive transverse enlargement so that it bulges out into pouchlike right and left chambers (Figs 416, 418). Although the beginning of the separation of these chambers from each other is clearly indicated as early as the fifth week by the presence of an interatrial septum, this septum is not immediately completed and the atrial chambers remain in communication below it by way of an opening called the primary interatrial foramen, or, more briefly, ostium I (Figs 418, B, 422, B).

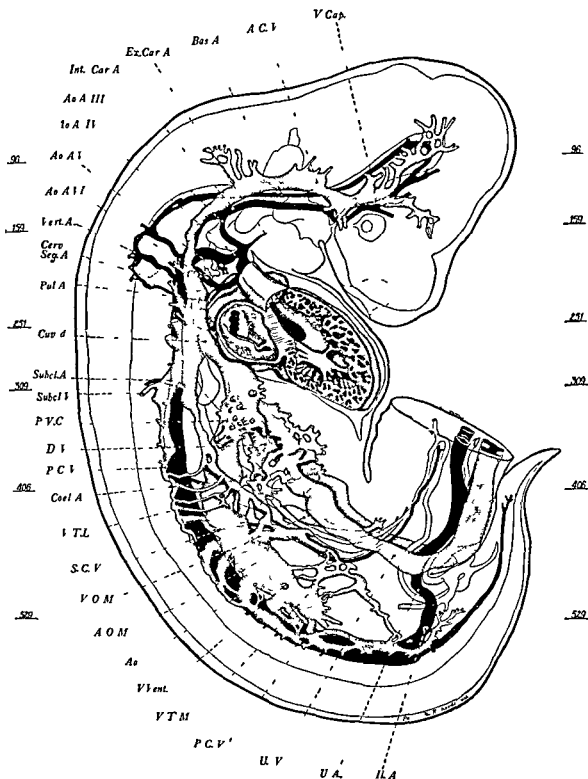
Leaving the atrium the blood passes to the ventricle through a constricted region known as the *atrio-ventricular canal*. At first a single channel (Figs 418, A, 422, A), in embryos of the fifth and sixth weeks this canal is, as was the case with the atrium, being divided into right and left channels. The division is effected by the so-called endocardial cushions of the atrio-ventricular canal. These cushions, located one dorsally and one ventrally in the walls of the canal, bulge into its lumen until they meet and fuse with each other, thus partitioning the canal into right and left channels (cf Figs 419, 420, 422).

The *ventricle* is formed from the most sharply bent part of the cardiac tube (Fig 73, C, D). In it, also, there are early indications of the impending separation of the heart into right and left sides. The *interventricular septum* appears as a well-marked median ridge growing from the apex of the ventricular loop toward the atrio-ventricular canal (Figs 418, B, 422, B-D). Above this septum, the two parts of the ventricle are still in open communication.

Correlated with its activity in pumping, the ventricular wall has become greatly thickened. Irregular branching bands of developing muscle tissue protrude from the main part of the wall into the lumen. These trabeculae carneae already suggest the muscular bands which project so characteristically into the cavities of the adult ventricles.

From the ventricle the blood passes into the *truncus arteriosus* and thence out to the body by way of the ventral aortic roots. Aside from the marked thickening of its walls, the truncus arteriosus shows little change from its original condition as the anterior part of the primitive cardiac tube. Its diameter remains small and the longitudinal division it is destined to undergo later in development (Fig 425, A) is barely suggested by the irregular shape of its lumen seen in cross-sections.

It should not be inferred from the modifications which have occurred in the different regions of the heart that it has as yet altered its primitive method

FIG 75 Reconstruction ($\times 14$) of circulatory system of a 9.4-mm pig embryo

A C V anterior cardinal vein
 Ao aorta
 Ao A aortic arch
 A O M omphalomesenteric artery
 Bas. A basilar artery
 Cery Seg. A intersegmental branches of aorta in cervical region
 Coel A coeliac artery
 Cur d common cardinal vein (Duct of Cuvier)
 D V ductus venosus
 Ex. Car A external carotid artery
 I L A iliac artery
 Int. Car A internal carotid artery
 P C V posterior cardinal vein

ABBREVIATIONS

Pul A pulmonary artery
 P V C posterior vena cava
 S C V subcardinal vein
 Subcl A subclavian artery
 Subcl V subclavian vein
 U A umbilical (allantoic) artery
 U V umbilical (allantoic) vein
 V Cap vena capitis (continuation of anterior cardinal vein)
 V O M omphalomesenteric (portal) vein
 V T L lateral transverse veins of mesonephros
 V T M medial transverse veins of mesonephros
 V Vent ventral vein of mesonephros
 Vert A, vertebral artery

vessels are formed between adjacent somites, they are known as the *dorsal intersegmental arteries* (Fig 74) Most of the important branches of the aorta arise either from these dorsal intersegmental vessels or from the other series of segmentally arranged branches which extend ventrally, and still others which extend laterally in the growing body (Fig 396) The development of these vessels into their adult arrangement is considered later, in the chapter on the circulatory system At the moment, we are interested only in becoming familiar with a few of the vessels that are especially conspicuous in young embryos

In the cervical region, the dorsal intersegmental vessels form a series of

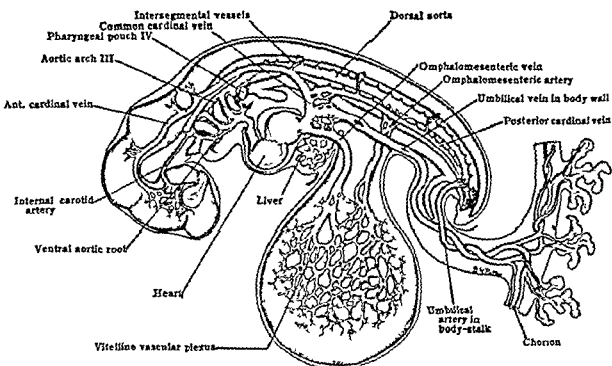


FIG 74 Semischematic diagram to show basic vascular plan of human embryo at end of first month For the sake of simplicity the paired vessels are shown only on side toward observer

connections with each other which eventually result in the establishment of the *vertebral arteries* (Figs 75, 392) Cephalic to the cervical level, the vertebral arteries are extended toward the mid-line and unite with each other to form a median vessel lying ventral to the myelencephalon This is the *basilar artery* (Figs 68, 75) Ventral to the cephalic flexure in the neural tube, the internal carotid arteries send branches mesiad to unite with the basilar This anastomosis between the internal carotids and the basilar is the first step in the formation of the *arterial circle* (circle of Willis) which is such a conspicuous landmark in the adult anatomy of the hypophyseal region (Fig 394)

At the level of the anterior appendage buds, the seventh pair of dorsal intersegmentals become enlarged as the start of the *subclavian arteries* to the arms Farther back in the body, the dorsal intersegmentals become the

and the posterior cardinal veins on either side of the body become confluent as the *common cardinal veins*, or *ducts of Cuvier*. The common cardinals are short trunks which at once turn ventro-mesial and enter the posterior part of the heart (Fig. 74).

In six-week embryos, little alteration from primitive conditions has occurred in the veins of the anterior part of the body. Numerous large tributary vessels have appeared, especially in the cephalic region where they converge on either side of the head as the so-called *venae capitis* (Fig. 75). It is already possible to recognize in the larger of these branches the primordial vessels from which the main venous sinuses of the adult cranial region are derived (Fig. 404). Fundamentally, nevertheless, these veins are but an elaboration of the original anterior cardinal system. From them the blood passes caudad along the less modified portion of the anterior cardinals to enter the heart by way of the ducts of Cuvier. A series of small tributaries (dorsal segmental veins) return to the cardinal veins the blood distributed by the intersegmental arteries. Near the point where the anterior cardinal vein enters the duct of Cuvier, a well-developed branch brings back the blood from the mandibular region. The vessel which thus returns the blood distributed by the external carotid artery is the beginning of the *external jugular vein* (Fig. 76). The anterior cardinal vein itself is later known as the *internal jugular vein*.

In very young embryos, the posterior cardinal veins are the only conspicuous venous channels draining the caudal half of the body (Fig. 74). By six weeks, however, new vessels have appeared, and, while the relative position of the posterior cardinals as vessels lying dorsal to the mesonephroi remains unchanged, much of the blood formerly returned by them now reaches the heart over new channels. As a result, the posterior cardinal veins in the mid-mesonephric region begin to undergo regressive changes. The new vessels which thus bring about the diversion of the blood from the posterior cardinals are the *subcardinal veins*. When they first appear, these vessels are but an irregular plexus, tributary to the posterior cardinals (Fig. 403, A). The organization of longitudinal channels in these plexuses establishes the main subcardinal veins as vessels extending cephalad in the ventromesial border of the mesonephroi, parallel with and ventral to the posterior cardinal veins. In the cephalic part of the mesonephros, the newly established subcardinal blood stream enlarges some of the small channels already entering the posterior cardinal and discharges through them into the posterior cardinal vein (Figs. 75, 403, B).

With the growth of the mesonephroi the rapidly enlarging subcardinal veins are brought very close to each other. Where they are approximated, cross-communication is established, first by small vessels (Fig. 403, B) and then by a broad *intersubcardinal anastomosis* (Figs. 65, 76, 403 C, D). The large median *subcardinal venous sinus* thus formed probably offers less resistance to the flow of blood than surrounding channels, in any case, all the vessels connecting with it tend to drain toward it.

One might expect that the great volume of blood entering the subcardinal

intercostal arteries, retaining even in the adult their original segmental arrangement (Fig 397)

When first formed, the dorsal aorta is, as we have seen, a paired vessel. This paired condition is retained in the branchial region, but caudally the two primitive aortae soon fuse with each other to form a median vessel (Fig 396). The fusion first occurs in the mid-body region and extends thence cephalad to about the level of the anterior appendage buds and caudad throughout the length of the aorta (Fig 68).

In young embryos, the most conspicuous vessels arising from the dorsal aorta ventrally are the *omphalomesenteric arteries* which are prolonged as the vitelline arteries to the yolk-sac, and the *allantoic* or *umbilical arteries* to the vascular plexus of the chorion (Figs 74, 398). These vessels arise from the aorta before its fusion, and, being derived by enlargement of its primitive ventral segmental branches at the levels concerned, are at first paired—right and left. The umbilical arteries retain their paired condition, but when the body is closed ventrally the right and left omphalomesenteric roots are brought together in the mid-line and fuse with each other to form a median vessel running in the mesentery (Fig 396). With the early degeneration of the yolk-sac, this vessel becomes relatively less conspicuous and is known as the *superior mesenteric artery* (Figs 68, 398). Its original relations are, nevertheless, apparent from its course along the intestinal loop into the belly-stalk to the place where the small yolk-sac still retains its attachment to the gut.

Somewhat cephalic to the superior mesenteric artery, the *celiac artery* arises in a similar manner and extends in the mesentery toward the gastric region of the gut tract (Figs 68, 398). In the adult, the celiac, superior mesenteric, and inferior mesenteric arteries constitute a group of vessels which one naturally thinks of together because of their similar ventral origin from the aorta, their course through the mesenteries, and their termination in the gastro-intestinal tract. The *inferior mesenteric artery* is still inconspicuous in six-week embryos. It arises from the aorta caudal to the other two enteric vessels in a similar manner but at a slightly more advanced stage of development (Fig 398).

At mid-body levels, the aorta gives off laterally many small *mesonephric branches*. These vessels feed the capillary plexuses (glomeruli) in the dilated ends of the mesonephric tubules and the network of capillaries which surround the tubules themselves (Fig 339). Individually, these branches are very small, but the volume of blood they handle collectively is surprisingly large as evidenced by the size of the veins (post- and subcardinals, Fig 403, A, B) which drain the mesonephroi.

Veins The main vessels serving to collect the blood which is distributed to all parts of the embryo by branches from the aortae are the cardinal veins. They arise by an entirely similar process, but become clearly defined somewhat later than the aortae. There are at first two pairs of these vessels, the *anterior cardinal veins* draining the cephalic, and the *posterior cardinal veins* draining the caudal region of the body. At the level of the heart the anterior

cardinal vein for a short distance, and thence, by the newly excavated channels in the mesentery, through the liver to the heart (Fig 403) The later changes involved in the formation of the embryologically composite inferior vena cava will be taken up in Chapter 19

Extra-embryonic Extensions of Circulation In addition to the vessels limited in their distribution to the body of the embryo, there are conspicuous

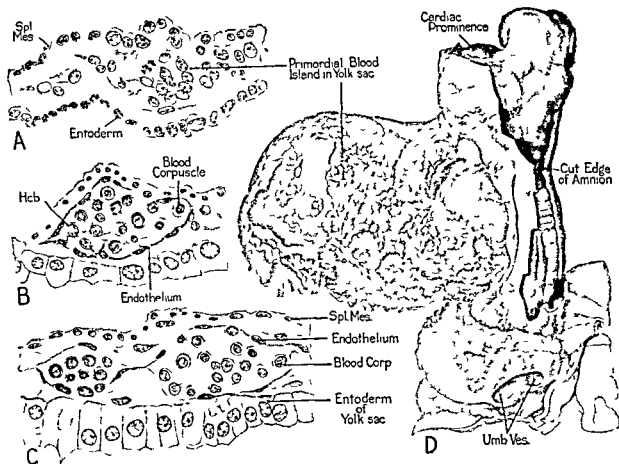


FIG 77 Development of yolk-sac blood islands. A-C are camera lucida drawings, reproduced $\times 355$. A, Early stage in aggregation of cells between endoderm and splanchnic mesoderm in yolk-sac of an embryo early in fourth week (17 somites). B, Beginning of differentiation of endothelium and primitive blood cells, from an embryo of about four weeks (4.5 mm). C, A more advanced area from a four-week embryo showing endothelium well differentiated and corpuscles suspended, free, in plasma. D, The Corner 10-somite embryo showing location of young blood islands on yolk-sac.

channels leading beyond the confines of the body to the yolk-sac and to the placenta. The main arteries from the aorta to the yolk-sac are called the omphalomesenterics and their terminal branches the vitellines. In the splanchnopleure of the yolk-sac, the main *omphalomesenteric vessels* are continuous with a rich plexus of small tributaries, the *vitelline vessels*. These smaller blood vessels can be traced into prevascular cords of mesodermal cells as yet not hollowed out. In these cellular cords are frequent knotlike enlargements, known as *blood islands* (Fig 77, A), containing not only cells which are destined to form vascular endothelium but also cells which will give rise to blood corpuscles. In the differentiation of a blood island the peripherally located

sinus would cause a corresponding enlargement of the anterior portion of one or both subcardinal veins. Instead, a new and more direct channel toward the heart appears. In its growth, the liver is crowded very close to the mesonephros. The developing liver contains a maze of vascular channels, as does

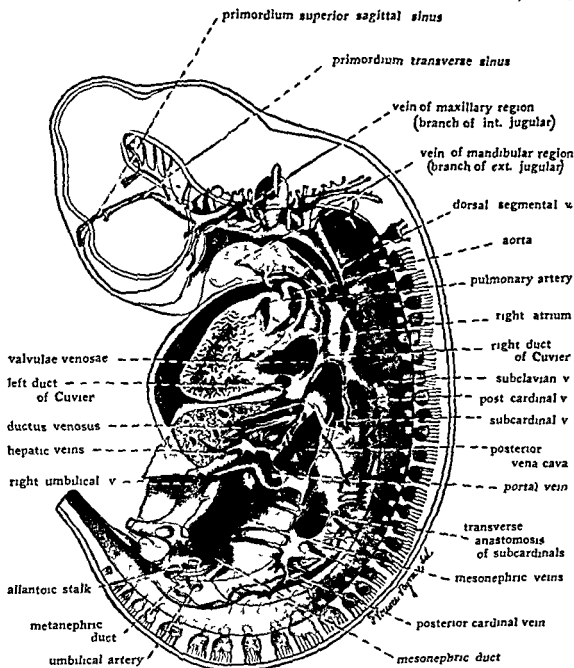


FIG 76 Reconstruction of 12-mm pig embryo showing relation of main venous channels to viscera (From Minot, after Lewis)

the mesonephros. Capillaries ramifying in the base of the mesentery between the liver and the mesonephros form the connecting link between the two organs. Once the blood begins to find its way by this route, the small irregular channels are rapidly enlarged and straightened to form the primordium of the *mesenteric portion of the inferior vena cava*. The new and more direct channel thus established leads from the subcardinal sinus through the right sub-

cardinal vein for a short distance, and thence, by the newly excavated channels in the mesentery, through the liver to the heart (Fig 403) The later changes involved in the formation of the embryologically composite inferior vena cava will be taken up in Chapter 19

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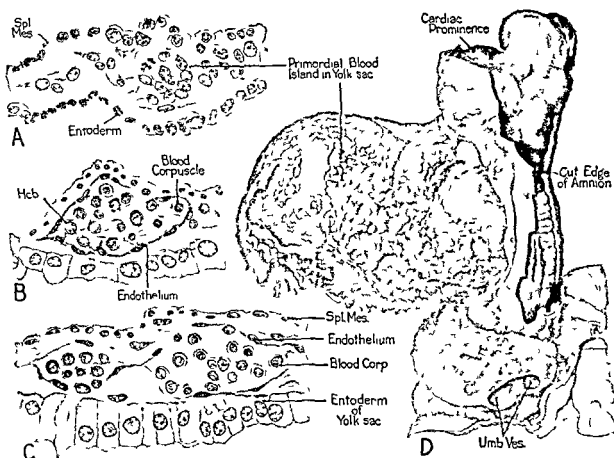


FIG 77 Development of yolk-sac blood islands A-C are camera lucida drawings, reproduced $\times 355$ A, Early stage in aggregation of cells between endoderm and splanchnic mesoderm in yolk-sac of an embryo early in fourth week (17 somites) B, Beginning of differentiation of endothelium and primitive blood cells, from an embryo of about four weeks (4.5 mm) C, A more advanced area from a four-week embryo showing endothelium well differentiated and corpuscles suspended, free, in plasma D, The Corner 10-somite embryo showing location of young blood islands on yolk-sac

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cells become flattened and somewhat separated from the rest of the mass (Fig 77, B) Eventually, they become arranged as a coherent investing layer, a single cell in thickness, and clearly endothelial in nature Meanwhile, fluid accumulates inside the endothelium and the inclosed cells which lay toward the center of the original mass become rounded and take on the characteristics of primitive blood corpuscles (Fig 77, B, C)

As the endothelial vesicles enlarge, they become confluent with similarly differentiating blood islands (Fig 77, C) with the resulting formation of a plexus of freely anastomosing endothelial tubes, the primordial capillary bed of the yolk-sac The collecting veins of the yolk-sac, known as the *vitelline veins*, become confluent in a pair of main veins passing from the yolk-stalk cephalad in close relation to the developing liver and discharging into the *sinus venosus* These main vessels are most properly called the *omphalomesenteric veins* (Fig 74), but this word is so cumbersome that the term vitelline veins is quite widely used to cover both the venous channels in yolk-sac walls and the main trunks by which they discharge to the heart

Two factors operate to change, at a very early stage, the original relations of the vitelline vessels As the reduced yolk-sac contributes less and less blood to them distally, they receive new tributaries proximally from the intra-embryonic portions of the gut tract At the same time, the growing liver encroaches on and breaks up their proximal portions so that instead of being returned to the heart by direct main channels the blood is routed through the maze of small channels ramifying among the developing cell cords of the liver We can see in these changes the beginnings of the portal circulation of the adult (Figs 406, 407)

Even more conspicuous than the vitelline vessels are those which constitute the second extra-embryonic extension of the vascular system—the allantoic circuit In human embryos, the allantoic diverticulum from the hindgut is small (Fig 70), but the allantoic mesoderm and vessels spread out on the inner face of the chorion just as they do in more primitive forms in which the allantoic lumen is capacious (Fig 78) This allantoic circulation, as we shall see when we consider placentation, becomes the embryo's channel of metabolic interchange with the maternal uterine circulation

The main arteries leading to the allantois are known either as the *allantoic arteries* from their destination, or as the *umbilical arteries* because they traverse the umbilical cord They arise from the caudal ends of the dorsal aortae when the aortae are still paired vessels Even after the primitive dorsal aortae have fused to form a simple median vessel, the umbilical arteries retain their original paired condition Passing along the belly-stalk, which is the forerunner of the umbilical cord, they branch out into small vessels terminating in the chorionic villi (Figs 74, 78)

The *allantoic* or *umbilical veins* which return the blood from the chorion to the heart are at first paired vessels traversing the belly-stalk and the lateral body-walls of the embryo (Figs 55, F, 74) Their original direct course through the body walls to the sinus venosus does not, however, long persist As was

the case with the vitelline circulation, the growing liver interrupts the umbilical veins. The underlying factor in this process is the extensive growth of the liver which brings it into contact with the lateral body-walls in which the umbilical veins are embedded. Fusion follows the contact and small vessels develop between the umbilicals and the network of channels in the liver (Fig 406, B). As these new vessels develop, the portions of the umbilical veins cephalic to them gradually drop out altogether and all the placental blood passes through the liver (Figs 75, 76, 406).

With the completion of this change in the umbilical circulation, the liver has become the common path of return for both of the original extra-embryonic circuits and most of the intra-embryonic circulation of the posterior half of the body. Only the dwindling current of the postcardinals and the unchanged anterior cardinal circulation now enters the sinus venosus without first traversing the liver. When we consider all this volume of blood passing through one organ, it leaves little room for surprise at the relatively enormous bulk attained by the liver in mammalian embryos.

The Three Arcs of Embryonic Circulation By way of a simplified summary, emphasizing its functional significance the early embryonic vascular system can be resolved into three distinct sets of afferent and efferent channels. Each set of these main channels, with its interpolated capillary beds, can conveniently be called a circulatory arc. One of these arcs we may designate as intra-embryonic. In this arc, the blood pumped by the heart is distributed by the aortae to the embryonic body. Small branches from the aortae break up locally into capillaries which bring the blood into intimate relation with the developing tissues, facilitating the passing on to them of oxygen and food materials, and relieving them of the waste products of their metabolism. The blood is then collected by the cardinal veins, and the other venous channels which later arise in association with them, and returned to the heart.

The other two arcs are the vitelline, which runs to the yolk-sac, and the allantoic or umbilical to the chorion (Fig 74). Both these arcs start within the embryo, for the heart serves as a common receiving and pumping station, and the aorta as a common distributing main, for all three of the circulatory arcs. But because their main vessels extend outside the body with their terminal ramifications in the extra-embryonic membranes, these latter arcs are ordinarily spoken of as extra-embryonic.

We see in the vitelline arc the strong imprint of phylogeny. The ancestral stock from which the higher mammalian types have evolved had a large yolk-sac well supplied with food material stored in advance by the mother. The development, in such forms, of a special circulatory arc by means of which this raw material for growth might be absorbed and transported from the yolk-sac to the body of the embryo for utilization was the logical outcome. Higher mammals, although no longer dependent on food stored as yolk for their growth, still go through the inherited motions of forming a yolk-sac and a vitelline circulation.

The allantoic arc is phylogenetically less ancient than the vitelline. Instead of being a regressing mechanism, as is the vitelline arc, it reaches its greatest development in mammals. In young mammalian embryos, it is the means of projecting embryonic vessels onto the inner face of the chorionic vesicle, thereby bringing the embryonic blood sufficiently close to the uterine blood of the mother to permit of the interchange of food, oxygen, and waste materials. It is but natural that this extra-embryonic extension of the circulation should appear very early and carry a relatively large amount of blood. It is on this arc that the yolkless embryos of higher mammals are dependent for the metabolic interchanges without which their development would be impossible.

Beginning of the Circulation of Blood It is naturally a matter of considerable interest to know when conditions in the growing circulatory system have progressed to a point which makes possible the propulsion of blood through the developing heart and vessels. No direct observations have been made on the beginning of the circulation of blood in man. But, reasoning from conditions known to exist in other embryos kept under continuous observation by tissue-culture methods, we would probably not be far astray in placing the first heart beats of the human embryo as occurring at about the transition from the third to the fourth week of development.

In chick embryos, where the first cardiac contractions and the beginning of the circulation of blood have been observed and recorded by micromoving-pictures, the first beats are spasmodic and interspersed with quiescent periods. There is a considerable interval between the time the first contractions of the growing heart muscle occur, and the beginning of the circulation of blood. One can, to speak figuratively, think of this as a period during which the heart is exercising itself and building up its contractile power until it is sufficient to set the blood in motion.

Meanwhile, corpuscles are being formed in the yolk-sac blood islands, and the venous channels leading to the heart can be seen to contain fluid. At first, this fluid is devoid of corpuscles, but just before the actual circulation of blood begins, a few corpuscles can be seen in the veins, freed from their parent cell clusters and shuttling back and forth with each heart beat. The heart has now apparently developed sufficient power to propel the blood, corpuscles are formed, and there is a fluid vehicle in the vessels. As soon as the gradually developing maze of small peripheral channels opens the connections between arteries and veins, a jerky progression of the corpuscles replaces their shuttling movement and the circulation of blood has commenced. If the sequence of events in the human embryo is comparable to that in the chick, it would be four or five days after the heart showed its first twitching before it set the blood in motion—probably some time early in the fourth week of development.

6

Fetal Membranes and Placenta

FORMATION AND PRIMARY RELATIONS OF FETAL MEMBRANES

In dealing with the establishment of the embryonic body, we have already seen that there are cellular layers extending far beyond the region in which the embryo itself develops. These peripheral membranes are of service during embryonic life as a means of protection and as a means of securing food and oxygen and eliminating waste materials. Because they are not incorporated in the body of the embryo but discarded at the time of birth, they are called extra-embryonic or fetal membranes. The extra-embryonic membranes that are common to the air-living vertebrates as a whole and may, therefore, be called primary are the yolk-sac, the amnion, the serosa, and the allantois. In higher mammals, in which the embryo receives no heritage of yolk, and is consequently dependent on establishing intimate relations with the maternal uterine circulation, the allantois and serosa are especially elaborately developed.

Although it is primarily the condition of the fetal membranes in human embryos in which we are interested, some of the relations of these membranes in less highly specialized forms help greatly in understanding the conditions in man. For the beautifully efficient organic mechanisms seen in higher forms do not appear suddenly out of nothing but are evolved by utilizing, either directly or with some new modification, structures already present in ancestral forms. Thus, the yolk-sac is essentially a dilated portion of the primitive gut, the amnion and the serosa arise as voluminous folds from the ventral body-walls, and the allantois is a distal extension of the primitive bladder. So, also, when we consider from this viewpoint the special organ of interchange between a mammalian embryo and its mother, known as the placenta, we find its fetal part developed from a combination of two of the primary fetal membranes, the allantois and the serosa. These membranes fuse to form the chorion, and the chorion then fuses with the lining of the uterus to form the placenta.

Yolk-sac In mammals, although there is virtually no yolk accumulated in the ovum, a yolk-sac is formed in the young embryo just as if yolk were present. Such persistence of a structure, in spite of the loss of its original function, is not an uncommon phenomenon in evolution, and has given rise to the biological aphorism that "morphology is more conservative than physi-

ology" Not only does the yolk-sac itself persist, but even the blood vessels characteristically associated with it in its functional condition appear in their ancient pattern in the walls of the empty yolk-sac of mammalian embryos (Fig 74) When the mammalian yolk-sac is spoken of as a vestigial structure, therefore, we must bear in mind that such a statement has reference primarily to its original function Morphologically, it is of considerable size in young embryos and its walls are an important temporary center of blood formation

The yolk-sac may be defined as that part of the primitive gut which is not included within the body when the embryo is "folded off" In dealing with the formation of the digestive tube, we have already sufficiently considered the processes which thus establish the boundaries between the yolk-sac and the intra-embryonic portion of the original gut cavity (Figs 70, 71) In the human embryo, the yolk-sac is most conspicuous between the ages of two and six weeks (Fig 79) By six weeks, it may attain a diameter of as much as 5 mm However, even at this stage it is being overshadowed rapidly by the relatively greater growth of the embryonic body In well-preserved chorionic vesicles of the second month, opened with due care, it may be seen in the region of the belly-stalk as a small vesicle at the end of a slender stalk (Figs 60, 61, actual size insets, lower right)

As the belly-stalk is inclosed in the amnion and transformed into the umbilical cord, the yolk-stalk is embedded in the cord, and the small yolk-sac is carried out to be caught between the amnion and the growing placenta (Figs 79, 85, C) Even in the full-term placenta, the yolk-sac, ordinarily concealed under the adherent amnion, usually can be located by careful dissection It then appears as a shrunken vesicle partly filled with detritus, lying not far from the insertion of the cord into the fetal face of the placenta (Fig 95, C)

Amnion In such forms as the chick (Fig 78, A) or the pig (Fig 78, B), the amnion arises as folds of extra-embryonic somatopleure which gradually envelop the growing embryo When the amniotic sac is completed, it becomes filled with a watery fluid in which the embryo is suspended This suspension of the embryo in fluid, by equalizing the pressure about it, serves as a protection against mechanical injury At the same time, the soft tissues of the growing embryo, being bathed in fluid, do not tend to form adhesions with consequent malformations That the functional significance of the amnion lies along such lines seems indicated by the fact that an amnion appears only in the embryos of non-water-living forms The amnion may be characterized, perhaps more picturesquely than scientifically, as a sort of private aquarium in which the embryos of air-living forms recapitulate the water-living mode of existence of remote ancestral types

All mammalian embryos form the amnion at a relatively early stage of development In human embryos, instead of arising by a leisurely series of foldings of the somatopleure as in the chick or pig, the amnion is formed, as it were, hurriedly and in a slurred-over fashion In fact, the amniotic cavity appears even before the body of the embryo has taken definite shape In the

youngest well-preserved human embryos so far recovered, the amniotic cavity is already recognizable as a minute space above the primordial cluster of cells destined to form the embryonic body (Figs 43-45) Its relations indi-

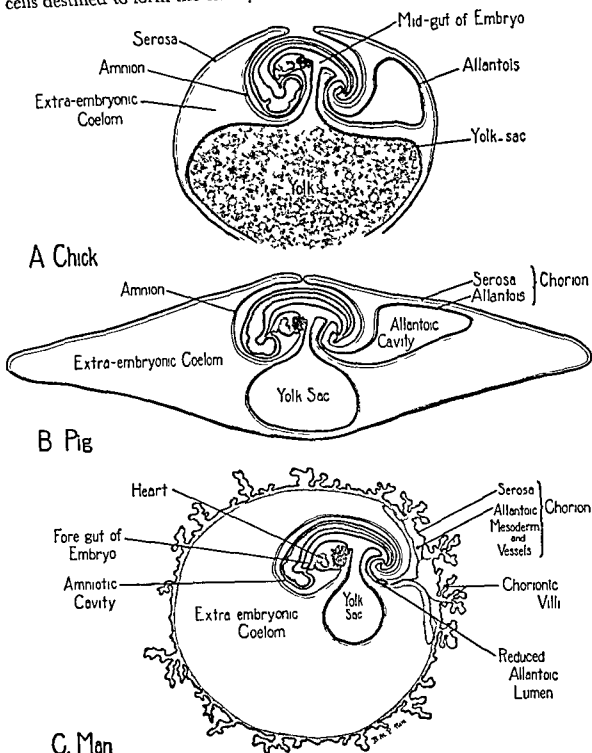


FIG 78 Diagrams showing interrelations of embryo and extra-embryonic membranes characteristic of higher vertebrates. Neither the absence of yolk from its yolk sac, nor the reduction of its allantoic lumen radically changes the human embryo's basic architectural scheme from that of more primitive types

cate that it must have arisen rather by cell rearrangement than by the sort of folding process seen in lower forms. Nevertheless, once it is established, its germ-layer composition, and its relations to the embryonic body and to the

other extra-embryonic membranes, leave no doubt as to the homologies of the primate amnion (Fig 78)

In young embryos, the amnion is attached to the body where the body-wall opens ventrally in the region of the yolk-stalk (Figs 70, 71, 79) As development advances, this ventral opening in the body-wall becomes progressively smaller, its margins being known finally as the umbilical ring Meanwhile, the yolk-stalk and the allantoic stalk, in the same process of ventral closure, are brought close to each other Together with their associated vessels, the yolk-stalk and the allantoic stalk then constitute the belly-stalk (Fig 79) The amnion, at this stage, as it is reflected from its point of continuity with the skin of the body at the umbilical ring, begins to cover the proximal part of the belly-stalk before recurving as a free membrane inclosing a fluid-filled space about the embryo

Still later in development, the amnion becomes expanded until it fills the entire extra-embryonic coelom (Fig 79, E) As it extends distally from the umbilical ring of the embryonic body, the amnion is now closely applied to the entire length of the belly-stalk, providing it with an epithelial covering The belly-stalk itself, meanwhile, is elongating rapidly and in its new configuration becomes known as the *umbilical cord* Thus, during the latter part of pregnancy, the amnion, distally, is reflected from the umbilical cord to the inner wall of the placenta to which it eventually becomes adherent (Figs 79, E, 92)

Serosa Because it was known descriptively long before its homologies were understood, the outer layer of the mammalian blastocyst has been called by various names In the inner-cell-mass stage of the embryo, the outer layer of the blastocyst is most commonly called the *trophoblast* The term is quite appropriate for the prefix *troph-* (Greek root = to nourish) suggests the part this layer is destined to play in the acquisition of food material from the uterus, and the suffix *-blast* takes into account its proliferative activities which are highly characteristic Another term for the same layer which emphasizes its homology with the serosal ectoderm of birds and lower mammals is *trophectoderm*

The trophoblast, or trophoctoderm, at a very early stage becomes reinforced by a layer of mesodermal cells, and recognition of this fact becomes necessary in its designation Two different terms may be used to cover this double outer layer of the blastocyst *Trophoderm* is widely used by those working especially in mammalian embryology where the importance of this layer in the nutrition of the embryo is so conspicuous Those especially interested in comparative embryology are quite likely to use the term *serosa* for this layer, thus emphasizing its evident homology with the membrane so designated in birds (Fig 78, A), reptiles, and lower mammals (Fig 78, B) These alternative names are not difficult to master if we understand they are both appropriate terms selected to emphasize somewhat different aspects of the same structure At this point, our interest should center on understanding this membrane as an extra-embryonic layer of somatopleure similar in germ-

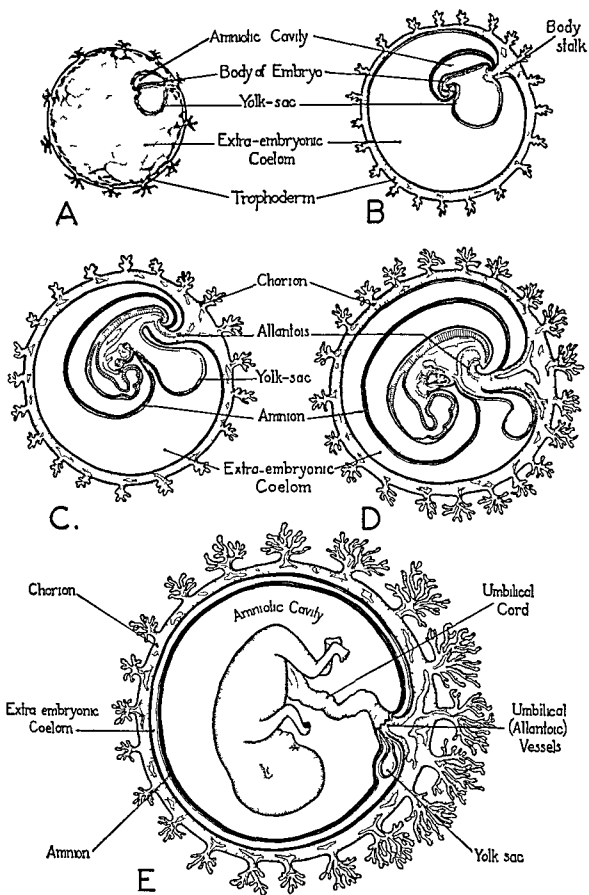


FIG 79 Early changes in interrelations of embryo and extra embryonic membranes

layer composition, and homologous in its relationships, with the serosa of more primitive forms. When the human chorion and placenta are discussed, the manner in which this membrane is involved in the establishing of fetal-maternal metabolic relations will call for more detailed consideration.

Allantois Almost as soon as the hindgut of the embryo is established, there arises from it a diverticulum known as the allantois. The allantoic wall, because of its manner of origin, is necessarily composed of splanchnopleure (Fig 70). In birds, reptiles, and most of the lower mammals, the distal part of the allantoic diverticulum becomes dilated into a sac which pushes out into the extra-embryonic coelom. The human allantois exhibits only a rudimentary tubular lumen confined to the belly-stalk region, but its mesoderm and blood vessels grow out beyond its lumen in a manner which is entirely comparable to the relations of the allantoic vessels in more primitive forms with a saccular allantois (Fig 78). Regardless of differences in its shape or in the size of its lumen, the allantois in its extension distally tends ultimately to come in contact with, and become fused to, the inner face of the serosa.

Chorion The term chorion is applied to the fetal membrane secondarily formed by the coalescence of the allantois with the serosa. In forms which have a saccular allantois (e.g., pig, Fig 78, B), the chorion is essentially a layer of allantoic splanchnopleure fused, mesodermal face to mesodermal face, with a layer of serosal somatopleure. In primate embryos where the lumen of the allantois is rudimentary, the formation of the chorion differs in that the entoderm is not involved. Allantoic mesoderm and vessels, however, extend distally beyond the rudimentary allantoic lumen and spread over the inner face of the serosa, establishing the same essential relationships as in less highly specialized forms (cf Fig 78, B, C). How far the allantoic lumen extends is of entirely secondary importance, for the chief functional significance of this fusion between the allantois and the serosa lies in the vascular relations involved.

In the lower mammals, to which we must look for an understanding of the origin of these essential relationships, the serosa is a thin membrane extending to relatively great distances from its site of origin from the ventral body-walls (Fig 78, B). Its primary vascular supply, as might be expected from these relations, is meager. Moreover, the manner in which the amnion arises from the inner limbs of the same folds which form the serosa (Fig 78, B) is of significance in this matter of blood supply, for when the amnion is pinched off as a separate sac, the original connection of the serosa with the embryo is so interrupted as to make mechanically difficult the maintenance of even the original small vascular connections.

It is the allantois that offers the solution to this impasse. As it grows out from the hindgut of the embryo, it early develops in its walls a rich plexus of vessels. This plexus, in turn, by large arteries and veins connects directly with the main circulatory channels within the embryo (Fig 74). The fusion of the allantois with the inner surface of the serosa, therefore, brings to this hitherto poorly vascularized layer an abundant circulation. In different groups of

animals, there are different details in the interrelations of the component parts of the chorion, and the chorion meets radically different environmental conditions. Nevertheless, the fundamental significance of this mechanism of vascularizing the outermost membranes of the embryo is the same. Whether it be a bird embryo dependent on this circulation for carrying on gaseous exchange with the outer air through the porous shell, or a mammalian embryo dependent on it for carrying on metabolic interchange with the uterus, does not change the essentials of the situation. The outermost investing membrane of an embryo is inevitably the layer most favorably situated for carrying on the business of interchange with the surrounding environment, and to profit by this interchange the embryo must have abundant vascular channels communicating with the site where these exchanges take place. If, in dealing with the chorion, attention is focused on these characteristic and vitally important vascular relations, and on the manner in which they are established, the fundamental homologies between the human chorion and other more primitive types of allantoic chorion are readily apparent. Only when undue emphasis is placed on such incidental matters as the size of the allantoic lumen is the picture clouded.

HUMAN FETAL-MATERNAL RELATIONS

Preparation of Uterus and Embryo for Implantation Having laid a foundation by learning something of the manner of origin and the interrelations of the primary extra-embryonic membranes and the chorion, we can now turn our attention more specifically to the relations of the human embryo and its membranes to the uterus. For successfully establishing itself in the uterus, it is essential that the embryo should arrive there at a favorable time. The general relations between ovulation and the cyclic changes in the uterus have already been outlined in connection with fertilization. It will be recalled that the time at which ovulation usually occurs in women is about 11 to 15 days after the onset of the preceding menstrual period (Figs. 24, 26). When fertilization occurs, it probably takes place shortly after ovulation, while the ovum is in the uterine tube near its fimbriated end.

On the basis of what is known of the process in other mammals, it seems probable that the human ovum takes from three to four days to pass through the tube. The precise mechanism of its propulsion is not, as yet, known with certainty. It seems doubtful that the action of the cilia of the epithelium lining the tube is alone responsible for moving the ovum, as was formerly supposed. Probably the muscular contractions of the tube, which are known to be increased in vigor at about the time of ovulation, are also of considerable importance. Whatever the significance of the cilia may be in propelling the ovum, another aspect of their activity must not be overlooked. By creating an outward movement of fluids in the uterine tubes, the cilia tend to furnish a certain degree of protection against ascending infections.

In most mammals studied, the passage of the ovum through the upper part of the tube seems to be relatively more rapid. It is not known whether the

retardation observed in the lower part of the tube is due to its smaller lumen, or to lessened activity of the tube because of the increasing interval since ovulation occurred, or to some other factor as yet unsuspected. Whatever may be the exact length of time involved, or the local variations in the rate of its progress, during its journey through the tube the ovum is undergoing cleavage. Presumably it arrives in the uterus as a young embryo in the morula stage (Fig 34, A, B). With reference to the uterine cycle, the time of the arrival of the embryo in the uterine cavity would be, on the average, about 16 to 18 days after the beginning of the preceding menstrual period. This is a time when the uterine mucosa has become greatly thickened, and its glands are becoming increasingly active—in other words, when it is coming into a favorable state for the reception of a young embryo.

But uterine preparation alone is not sufficient for implantation. The embryo itself must be in a condition to take advantage of the favorable nesting place. If it is like other mammalian embryos, when it first arrives in the uterus the young human embryo is still incased in a thick protective membrane, the zona pellucida. This means that the outer layer of cells by which its attachment is effected can not as yet even make direct contact with the uterine lining. Following its entrance into the uterus, there appears to be a period of about five or six days during which the embryo remains unattached in the uterine cavity. It seems probable that during this time the embryo is dependent for its nutrition on the glycogen-containing secretion of the active uterine glands. Human embryos during this unattached period and in the earliest phases of attachment have not as yet been secured for study, but fortunately the brilliant work of Heuser and Streeter on these stages in monkeys gives us a very circumstantial picture as to what the corresponding stages are probably like in man.

The first striking change in the embryo during the period it spends in the uterus before implantation is the hollowing out of the morula by cell rearrangement. In this process there is formed the so-called blastodermic vesicle (Fig 34, C–E). We have already traced the development of the inner cell mass of such a vesicle into the primitive embryonic body and the closely associated amnion and yolk-sac. From the standpoint of embryonic preparation for implantation, the disintegration of the zona pellucida (cf Fig 34, D, E) is the most significant event. This allows rapid expansion of the trophoblast layer, and permits its cells for the first time to make contact with the uterine lining.

FIG 80 Photomicrographs showing implantation of monkey embryo (After Heuser and Streeter, *Carnegie Cont. to Emb.*, Vol 29, 1941) A, Section ($\times 350$) of embryo of ninth day showing its initial adhesion to uterine epithelium. B, A nine-day embryo attached to uterine mucosa, viewed from above, $\times 50$. C, Same embryo photographed from the side, $\times 50$. D, Same embryo shown in B and C after sectioning, photomicrograph $\times 200$. E, Embryonic area of same embryo, photomicrograph $\times 500$. F, A ten day embryo beginning to invade the uterine mucosa, photomicrograph $\times 200$.

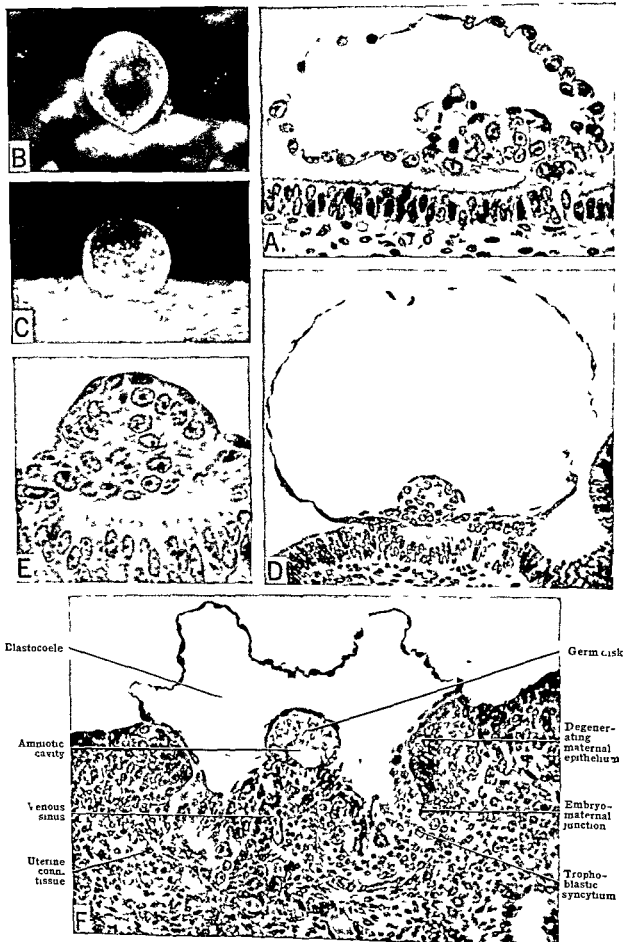


FIG 80 (For legend see p 146)

Implantation When freed from the zona pellucida, the trophoblast cells of the living blastodermic vesicle handled in physiological saline solution are noticeably sticky. This characteristic appears to be most marked in the cells directly overlying the inner cell mass, and the blastodermic vesicle tends to adhere by this part of its surface to the uterine lining (Fig 80, A-C). The initial point of adhesion is rapidly extended (cf Fig 80, A, D). In this process, there may be small areas of less intimate adhesion (Fig 80, D, E), leaving, for a brief time, tiny vesicular spaces between the embryo and the uterine lining. Such spaces, however, are very short-lived, for almost as soon as adhesion has occurred the trophoblast begins to proliferate rapidly and to erode the underlying uterine mucosa (Fig 80, F). In this process the small, irregularly shaped capillaries (sinusoids) of the uterine mucosa are opened and maternal blood oozes into the tissue spaces adjacent to the growing trophoblast cells of the blastodermic vesicle (Fig 81). The invasion of the uterine mucosa, thus commenced, progresses very rapidly. In a carefully timed series of monkey embryos, the first adherence of the blastocyst to the uterine lining was found to occur on the ninth day after fertilization, the burrowing process was far advanced on the tenth day, and by the eleventh day the embryo had completely buried itself in the uterine mucosa.

Recently Hertig and Rock have recovered a human embryo in a stage of implantation closely similar to that shown for the monkey in Fig 80, F. It was shortly after implantation occurred that these same workers had previously (1941) secured two of the best-preserved young human embryos as yet recovered. The younger of these specimens is estimated to have a fertilization age of about 10 or 11 days. It appears to have been implanted in the endometrium for little more than a day or two because, on the basis of what happens in the monkey, it should take just about that time after its first attachment for the embryo to become completely buried in the mucosa (Fig 41). Moreover, the clinical history indicates about such an age, and the general structure of the embryo (Fig 43) is closely similar to monkey embryos known to be of that age.

The patient from whom the specimen was obtained had been under observation for some time for a condition which finally made removal of the uterus advisable. Since the possibility of an early pregnancy was suspected at the time of operation, the removed uterus was opened with unusual care. Because of the uniqueness of the specimen obtained, the authors' description of its appearance in the fresh condition is quoted verbatim: "On the posterior wall

1.2 cm from either lateral margin of the uterine cavity, and 6 mm from its posterior boundary, was a slightly raised, pale gray, glistening, translucent area slightly less than 1 mm in diameter, interpreted as the implanted ovum" (Hertig and Rock, 1941, p. 132). The adjacent area of the endometrium was markedly reddened due to the extravasation of blood from the sinusoids which had been opened by the invading trophoblast (see Fig 83). This reddened area appears dark in the photograph here reproduced as Fig 82, A. The uterine

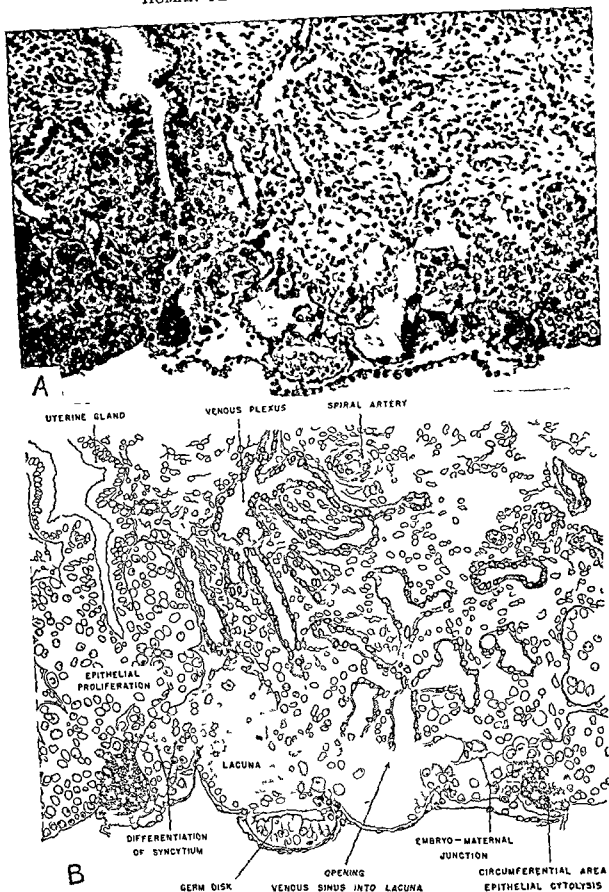


FIG 81 Monkey (macaque) embryo and implantation site at end of tenth or beginning of eleventh day after fertilization (After Heuser and Streeter, *Carnegie Cont to Emb*, Vol 29, 1941) A, Photomicrograph $\times 150$ B, Explanatory diagram of photomicrograph shown in A. The thin trophoblastic wall of the blastocyst shown in A collapsed against the inner cell mass has been omitted in the explanatory diagram to make room for labels

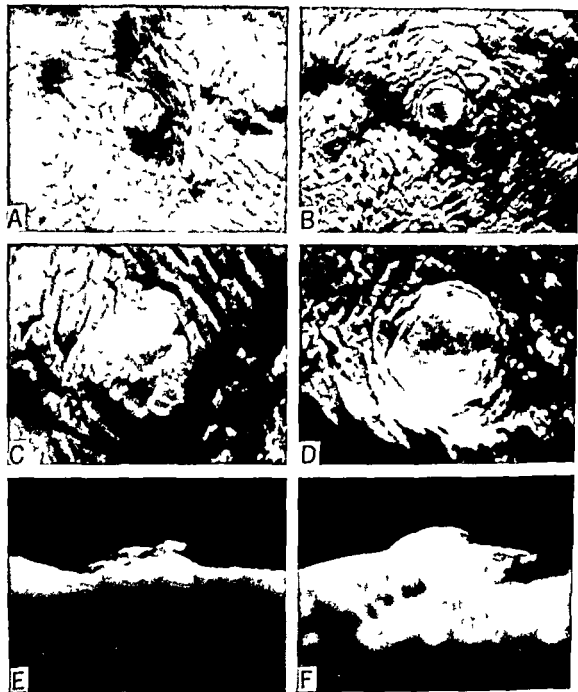


FIG 82 Photomicrographs of implantation sites of very young human embryos (After Hertig and Rock, *Carnegie Cont to Emb*, Vol 29, 1941) A, Surface view, $\times 8$, of uterine mucosa at implantation site of embryo 7699, Carnegie Collection, estimated fertilization age 11 days B, Surface view, $\times 8$, of uterine mucosa at implantation site of embryo 7700, Carnegie Collection, estimated fertilization age 12 days C, Same specimen and view as A, $\times 22$ D, Same specimen and view as B, $\times 22$ E, Same specimen as A, side view, $\times 22$ F, Same specimen as B, side view, $\times 22$

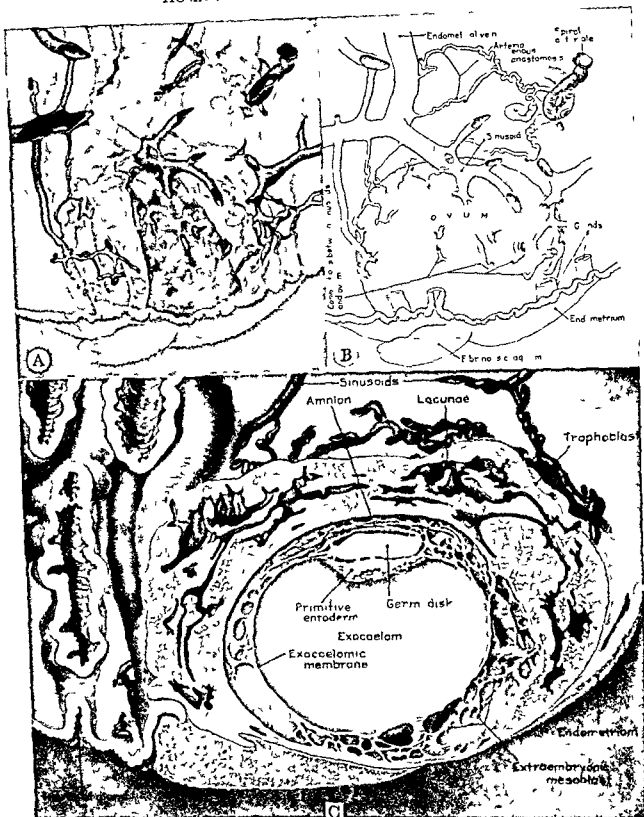


FIG 83 Reconstructions of Hertig-Rock Embryos to show their relations to uterine blood vessels A, General relations of embryo 7699 (\times about 62.5) B, Key to A C, Reconstruction of embryo 7700 (\times about 115) opened in sagittal plane (From Hertig and Rock, *Carnegie Cont. to Emb.*, Vol 29, 1941)

mucosa had reclosed over the embryo and there remained only a minute protruding tag of coagulum (Fig 82, E) marking the point of penetration

Development of Chorionic Villi Once the embryo is implanted, there follow rapid and profound changes in both the chorion and the endometrium. Although these changes are concomitant, their significance will be somewhat more readily understood if the earlier changes in the chorionic villi are followed before attention is directed to the uterine changes and to the relations of the villi to the endometrium

The primordial cell masses from which the chorionic villi are derived consist at first merely of proliferating clusters of trophoblast cells. As certain

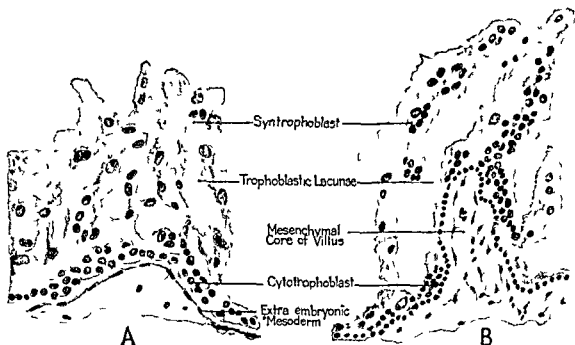


FIG 84 Early stages in development of chorionic villi A, Primitive trophoblastic projection without mesenchymal core (Redrawn, $\times 225$, from Streeter's photomicrographs of the Miller embryo) B, Young villus just developing a mesenchymal core (Redrawn to about the same scale as A, from Fischel's figure of an embryo in the primitive streak stage)

of the cells of trophoblastic origin are pushed peripherally, they lose their cell boundaries and are spoken of as constituting the *trophoblastic syncytium* (Figs 43, 44, 84, A). Although these trophoblastic cell masses increase rapidly in extent, their early growth habits give rise to sprawling, anastomosing strands inclosing irregular spaces called lacunae (Figs 43, 84, A) rather than to anything suggestive of the typically shaped branching villi of older stages (Figs 88, 89). This early condition of the trophoblast is sometimes described as "previllous."

As embryos approach the end of the second week, the trophoblast begins to be molded into masses more suggestive of villi. These very young villi at first consist entirely of epithelium, with no connective-tissue core. In this stage, they are referred to as primitive (or primary) villi (Fig 84, A). Their differentiation is very rapid, for even the previllous cell masses are already

beginning to show two types of cells. The outer cells become large, lose their intercellular boundaries, and run together in a syncytium called the syncytotrophoblast (plasmotrophoblast), while the deeper-lying cells which constitute the so-called cytotrophoblast (Langhans' layer) remain smaller and maintain distinct boundaries.

The phase in which the developing villi lack a mesenchymal core is very short-lived. While the primitive villi have been forming, the inner face of the blastodermic vesicle has been receiving an ingrowth of allantoic vessels and mesoderm. Early in the third week after fertilization, the mesoderm pushes into the primitive villi so that the trophoblastic cells, instead of constituting the whole structure, become a covering epithelial layer over a framework of delicate connective tissue derived from the mesodermal ingrowth (Fig 84, B). Blood vessels soon appear in the connective-tissue core of the villus and push out into its newly formed branches. Such villi, with a vascular connective-tissue core, are called "true" chorionic villi. This condition in which the villi are prepared for their absorptive function is reached by about the close of the third week. The villi retain this same general structural plan throughout pregnancy, although as gestation advances their connective-tissue core and blood vessels become more highly developed and there are marked regressive changes in their epithelial covering (Fig 87).

Invasion of Endometrium The invasive proclivities of the trophoblast continue actively for some time after the initial penetration of the endometrium. As the primary villi grow out, they destroy the adjacent maternal tissue, probably through the action of some sort of proteolytic enzyme produced by the trophoblast cells constituting their outer layer. This process makes more room for the growing chorionic vesicle, and it seems not improbable that the liquefied material from the disintegrating uterine cells may be utilized in the nutrition of the embryo pending the time when a more efficient mechanism of vascular interchange is established. On this assumption, the liquefied material is commonly called "*embryotroph*."

Whatever the importance of the *embryotroph* may be for temporary nutrition, the invasion of the endometrium rapidly paves the way for establishing the type of vascular interchange on which the embryo is to be dependent for the rest of its intra-uterine life. As the trophoblast of the growing villi spreads out into the uterine mucosa, it inevitably comes into contact with small blood vessels and breaks down their walls. While apparently the ameboid trophoblast cells tend to dam the opened vessels somewhat and check excessive extravasation of blood, there must, nevertheless, be continued oozing from the invaded vessels, for the trophoblast is known to produce some substance which inhibits the coagulation of blood. In addition, there is transudation of blood serum and lymph so that the invading villi come to lie in eroded areas of endometrium, saturated in maternal blood and lymph. By this time, the villi themselves have become vascularized, as described above. The small vessels of the villi are in open communication with the main intra-embryonic blood channels by way of the allantoic arteries and veins (Fig 74). It remains

only for the embryonic heart to start the blood circulating, and the entire elaborately interlocking mechanism for the nutrition of the embryo is ready to go into operation. As was pointed out in discussing the early appearance of the vascular system, we can place the time of the establishing of the human embryonic circulation as being toward the close of the third or beginning of the fourth week after fertilization, or approximately 10 or 12 days after its implantation.

Formation of Placenta Under the influence of the presence of an embryo, striking changes take place in the endometrium. These are most marked, naturally, at the site of implantation, but the entire uterine lining is affected in one way or another. Thus it is not surprising that at the termination of pregnancy the endometrium is extensively sloughed off and then rebuilt. This postpartum phenomenon of its shedding and replacement has given rise to the term *decidua* (root meaning, to shed) for the endometrium of pregnancy.

The fact that the human embryo promptly burrows into the endometrium, instead of becoming merely adherent as is the case in certain other mammals, establishes at the outset positional relationships which shape the later course of events. As the chorionic vesicle grows, the overlying portion of the endometrium is stretched out over it, forming a layer known as the *decidua capsularis* (Fig 85). The portion of the endometrium lining the walls of the uterus elsewhere than at the site of attachment of the chorionic vesicle is called the *decidua parietalis*. The area of the endometrium directly underlying the chorionic vesicle is termed the *decidua basalis*.

The absence of chorionic villi in the decidua parietalis obviously leaves this part of the endometrium with no direct rôle to play in the nutrition of the embryo. It is equally obvious that the maternal blood supply is most direct and abundant in the decidua basalis. Conditions in the decidua capsularis vary considerably at different ages. At first, the chorion underlying this part of the decidua is as well supplied with villi as any other region (Fig 85, A), but, before long, the growth of the chorionic vesicle causes the decidua capsularis to be pushed away from the maternal vascular supply. Moreover, the tissue of the decidua capsularis itself becomes more and more attenuated as the chorionic vesicle increases in size. These unfavorable conditions in the decidua capsularis are promptly reflected in the less exuberant growth of the chorionic villi embedded in it (Fig 85, C). Thus the relations established when the chorionic vesicle first buried itself in the endometrium lead toward the decadence of the villi in a large part of the chorionic vesicle.

In contrast with the chorionic villi in the region of the decidua capsularis, the villi adjacent to the decidua basalis grow with increasing vigor. Here is, unmistakably, the part of the mechanism most effectively situated for carrying on metabolic interchange between the fetus and the mother. By the third month, when the growth of the embryo begins to compress the decidua capsularis and parietalis against each other, the villi begin gradually to disappear altogether from this area. Thus the chorionic vesicle, at first uniformly villated over its entire surface, has by the end of the fourth month become denuded of

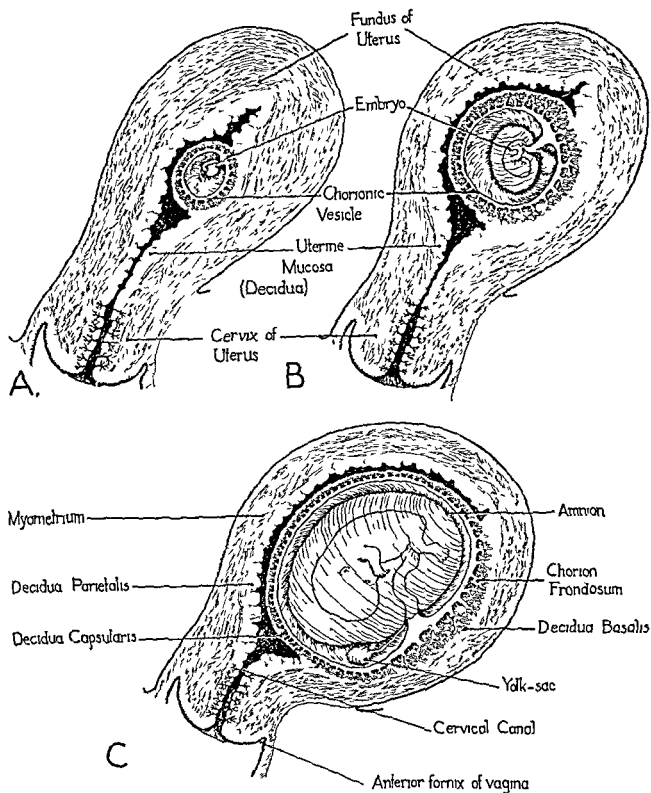


FIG 85 Diagrams showing uterus in early weeks of pregnancy. Embryos and their membranes are drawn to actual size. Uterus is within actual size range—about correct for a small primipara. A, At three weeks; B, At five weeks; C, At eight weeks fertilization age.

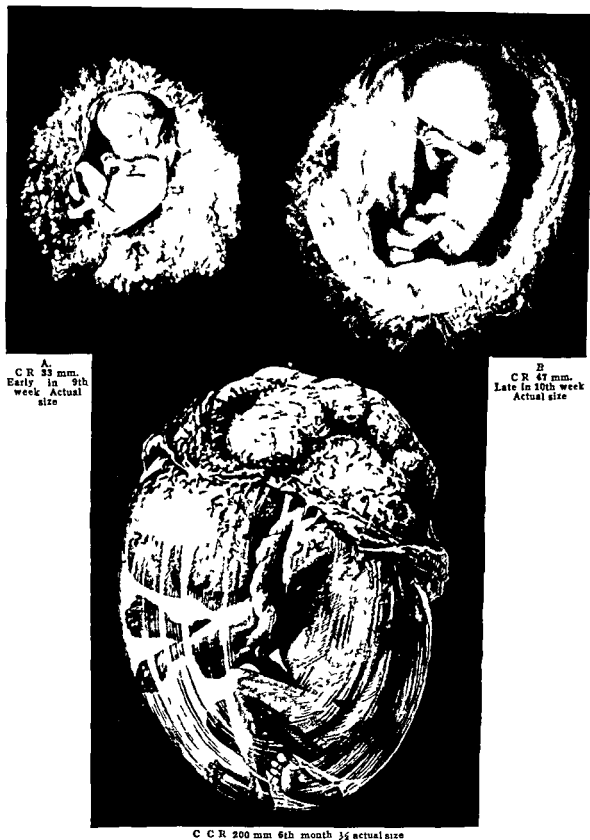


FIG 86 Embryos and their membranes at three different stages of development A, University of Michigan Coll, EH 217 B, University of Michigan Coll, EH 152 C, Redrawn from Kollmann

its villi everywhere except where they lie in the decidua basalis (Figs 85, 86, 92) The part of the vesicle under the decidua capsularis which has thus lost its villi becomes known as the *chorion laeve* (smooth), and that part of the chorion next to the decidua basalis where the villi are highly developed is termed the *chorion frondosum* (tufted or bushy) It is the interlocked chorion frondosum and decidua basalis which together constitute the *placenta* This dual origin of the organ of metabolic interchange between embryo and mother is emphasized in the Latin terms *placenta fetalis*, which is just another name for the chorion frondosum, and *placenta materna*, which is merely another designation for the decidua basalis

Later Changes in Structure of Uterus and Placenta From their first invasion of the uterine lining, the chorionic villi lie in excavated spaces in the endometrium, bathed in maternal blood and lymph (Fig 83) Essentially, this relationship is retained throughout pregnancy, but the extent of the blood spaces, the relations of the villi to the endometrium, and the structure of the villi themselves, are all modified in detail as development progresses During the first few weeks after implantation, the invasion of the endometrium is exceedingly rapid, and the area which is becoming decidua basalis is progressively extended (Fig 85) In this period, the syntrophoblast is very conspicuous, forming sprawling, branching processes extending into the endometrium far beyond the main mass of the chorionic vesicle By the third week, the placenta involves about one-fifteenth of the internal surface of the uterus At the end of the eighth week, the placental area has become nearly a third of that of the uterus Its greatest relative size is reached during the fifth month, when the placental area is roughly half that of the interior of the uterus In the last months of pregnancy, the relative expansion of placental area is less rapid, although its absolute growth continues and it becomes as much as three or four times the thickness it had reached at mid-pregnancy

Once the chorion has become well established in the uterus, the invasive process becomes relatively slower, merely keeping pace with the growth of the embryo The slower rate of invasion is reflected in a reduction of the syntrophoblast to form a more regularly arranged covering outside the cytotrophoblast layer of the villus Meanwhile, the mesenchymal core of the villus has become organized into a delicate connective tissue supporting the endothelial walls of the blood vessels so that the entire villus takes on a much more definitely organized appearance (Fig 87) Scattered in the connective tissue there appear, in variable numbers, cells which are conspicuously larger than the ordinary connective-tissue cells These have been given the name of *Hofbauer cells*, after the man who first described them Their significance is not as yet entirely understood, but they appear to be phagocytic and are commonly believed to act as a primitive type of macrophage

In the established parts of the placenta, the invasive function of the epithelial covering of the villi ceases to be important and the epithelial layers become relatively thinner The cytotrophoblastic layer reaches the height of its development during the second month (Fig 87, B) Thereafter, it gradually

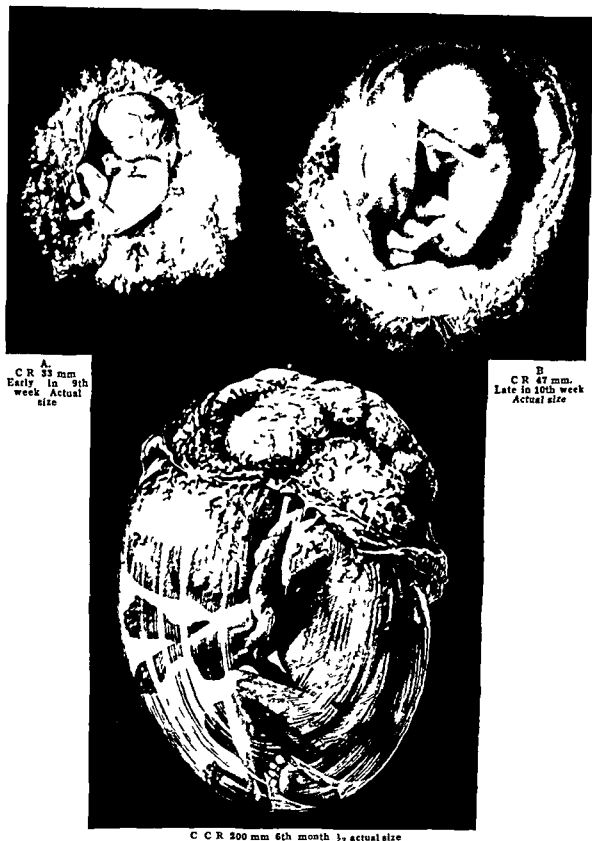


FIG 86 Embryos and their membranes at three different stages of development A, University of Michigan Coll, EH 217 B, University of Michigan Coll, EH 152 C, Redrawn from Kollmann

loses its completeness (Fig 87, C) It is as if this layer spent itself in the production of the syncytial layer During the fourth and fifth months, the cytotrophoblast layer undergoes still further regression Most of the villi come to be clothed in a reduced syntrophoblast layer with only occasional cytotrophoblastic cells persisting During the last third of the period of gestation, this process becomes more marked, but if material is freshly secured and properly fixed it will be seen (Fig 87, D) that the villi do not become as completely denuded of epithelium as was formerly believed

In clinical work, a knowledge of these characteristic changes in the chorionic villi at different stages of pregnancy is of considerable importance in the

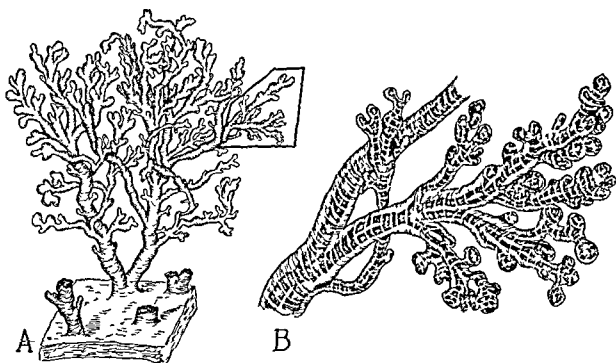


FIG 88 Human chorionic villi (Redrawn after Corning and Kollmann)
A, Reconstruction to show branching of villi B, Terminal villi, such as those enclosed by marking in A, more highly enlarged and injected to show blood vessels

examination of uterine curettings From the standpoint of functional significance in the development of the embryo, one would stress the exuberant development of the trophoblast during the period of invasion, followed by the gradual reduction of the epithelial layers of the villi after their invasive rôle has been carried out, and the thinning thereby of the amount of tissue through which the interchanges between fetal and maternal blood take place ¹ Whether or not the epithelium, after its invasive phase, carries on any intermediary action of a digestive-absorptive type remains an interesting field for future investi-

¹ The term 'placental barrier' is coming into rather general usage, particularly in the clinical literature to cover all the tissues through which substances must pass in the interchanges which go on between fetal and maternal blood With the discovery of the Rh factor involved in fetal erythroblastosis, and the possible damaging effect on the fetus of the virus causing German measles in the mother (see section on abnormalities of eye development), increased interest must center on the exact nature of the placental barrier and on any possible selective action it may have in holding back certain substances while permitting others to pass

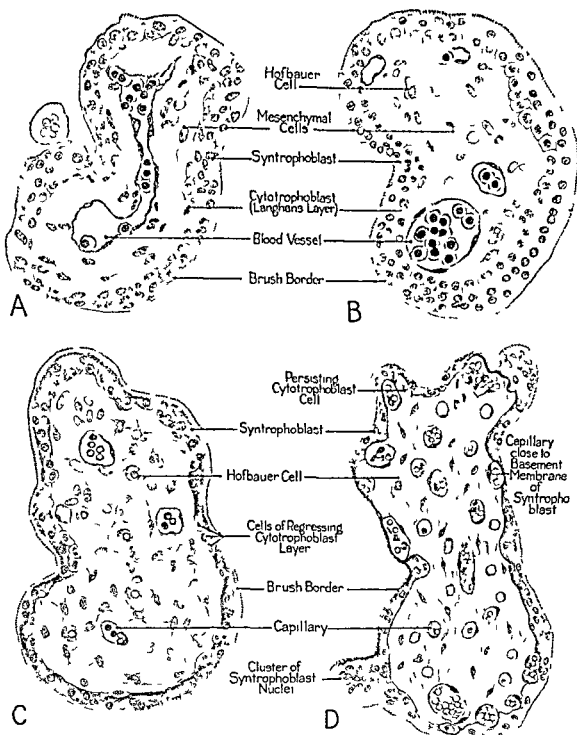


FIG 87 Chorionic villi at various ages (Camera lucida drawings $\times 350$)
 A, From chorion of four-week embryo (C-R 4.5 mm) B, Chorion from an embryo of about six and a half weeks (C-R 15.1 mm) C, Placenta from a fetus of the fourteenth week D, Placenta at term (From preparation loaned by Dr Burton L. Baker)

ledons Between the cotyledons, the maternal tissue has been less deeply eroded and constitutes the so-called *placental septa* (Fig 89) Between the septa the tips of most of the villi lie free in the space which has been excavated in the uterine mucosa The tips of other villi make contact with the uterine tissue at the bottom of the excavation and their trophoblast spreads over the eroded uterine surface to form the so-called trophoblastic shell As development progresses, some of these villi become especially intimately related to the maternal tissue The trophoblast over their tips disappears and the connective



FIG 90 Photomicrograph ($\times 60$) of injected placenta at term

tissue of the distal ends of these "*anchoring villi*" becomes actually adherent to the endometrial connective tissue Most of the villi lie more or less free in excavated spaces in the decidua basalis Maternal blood enters the spaces about the villi from the numberless small vessels which were opened in the excavating process As this blood drains back into the uterine veins, it is replaced by blood supplied by way of the uterine arteries, so that the villi are continuously steeped in fresh maternal blood

One must be careful not to acquire ideas too far from reality by perusing a highly schematized diagram such as Fig 89, which aims to show merely a simplified plan of placental relations In actual sections (Fig 90), one finds a bewildering maze of branching villi inextricably mixed with irregularly shaped, persisting portions of endometrium One looks in vain for the capacious "blood pools" of the diagrams until they are recognized in the form of the minute crevices between maternal and fetal tissue Nor is the blood in which the villi are bathed brought in or drained off by any such wide-open

gation Challenging, also, is the problem of the mechanism involved in the cessation of invasion. Some investigators see in the phenomenon a nicely balanced co-operation between fetal and maternal tissues, whereas others—probably a matter of bellicose temperament—see the trophoblastic growth as an invasion, and interpret its checking as the result of a counter-attack on the part of the maternal tissues. Such differences in approach serve to bring the

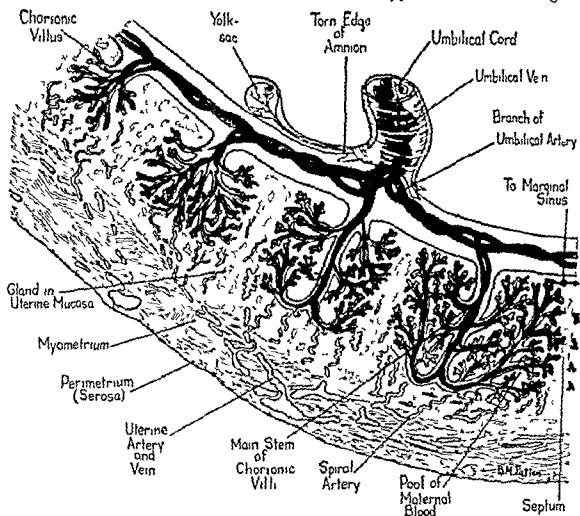


FIG 89 Schematic diagram to show interrelations of fetal and maternal tissues in formation of placenta. Chorionic villi are represented as becoming progressively further developed, from left to right across the illustration. Maternal vessels are conventionally colored, fetal arterial branches are shown in dark wash, and fetal venous branches in gray wash.

problem into focus, but add nothing to our knowledge of the actual mechanisms involved.

The relations of the villi to the endometrium and to the maternal blood stream are attained as the logical conclusion of the early invasive activity and later specializations which we have just been tracing. As pregnancy advances, the villi grow greatly in size, and the complexity of their branching increases (Fig 89). If we likened them to trees we would find them growing over the discoidal area of the chorion frondosum not quite uniformly, but in about 15 to 16 dense clumps. These main concentrations of villi are known as coty-

an exaggeration of the premenstrual changes already well under way when implantation occurred. Menstruation is, however, suppressed by the pregnancy and the later changes in the decidua are unlike those occurring in the menstrual cycle. Moreover, because of radically different relations to the growing embryo, the changes in the different regions of the decidua show certain special characteristics.

When the growth of the embryo begins to compress the decidua parietalis, it becomes so changed in appearance it is difficult to realize, in looking at sections, that it has been formed by modification of the mucosal structures of the nonpregnant uterus. The surface epithelium degenerates almost completely. The superficial portions of the glands also degenerate so that their deeper portions remain as blind pockets. As the uterus is expanded to accommodate the increasing size of the growing embryo, the deep portions of the glands become pulled out to form flattened openings parallel to the surface. This condition of the glands is of particular interest because it is along the line of their slit-like lumina that the decidua separates when the bulk of it is discarded as part of the "after-birth."

A peculiar histological feature of the endometrium of pregnancy, worth commenting on because of its diagnostic significance in the examination of curettings, is the presence of enlarged cells known as *decidual cells*. These decidual cells apparently arise by modification of certain of the connective-tissue cells. They are not ordinarily strikingly differentiated until the second month. Thereafter they become for a time increasingly abundant and more readily recognizable because of their conspicuous size and irregular shapes (Fig 91, B). Their general appearance is usually characterized as epithelioid. At the height of their development, they range in size from 30 microns up to as large as 100 microns (Fig 91, C). Not infrequently, the larger cells show more than one nucleus. During the final trimester of pregnancy, the decidual cells become smaller and many of them degenerate.

The part of the chorion not involved in the formation of the placenta also undergoes interesting changes. During the last half of pregnancy, the chorion laeve is pushed by the growing embryo tight against the uterine walls. The chorion brings with it, on its external surface, what remains of the much thinned out and atrophic decidua capsularis (Fig 92). This is squeezed against the decidua parietalis and gradually fuses with it. Adherent to the inner face of the chorion laeve is the amnion, which during the third month expands to fill the entire chorionic sac (Fig 79) and soon thereafter becomes loosely attached to its inner face. Thus a section passing through the tissue between the amniotic cavity and the muscular layer of the wall of the uterus, in a region clear of the placenta, will show a fusion of four originally separate structures. From the embryo toward the uterus these are, in order, the amnion, the chorion laeve, the decidua capsularis, and the decidua parietalis (Fig 92). The two middle layers are compressed almost beyond recognition. In fact, one would have great difficulty during the last third of pregnancy in identifying the decidua capsularis at all.

vessels as those shown in diagrams. Rather, there is a constant slow oozing into the spongelike placenta from a myriad of small vessels, the walls of which have been more or less opened by trophoblastic erosion. The slowness of this flow is favorable for the interchange of materials between the fetal and maternal circulations, but, as is so often the case with arrangements advantageous from one special standpoint, it entails its own peculiar hazard of increased likelihood of coagulation. Undoubtedly, the flow from opened or partly opened vessels is supplemented by much seepage of plasma and lymph from unopened maternal vessels in the vicinity. Notwithstanding all these details, a simplified plan of structure such as that worked out in Fig. 89 serves very well to emphasize the significance of the intricate interlocking of fetal and maternal tissues in the placenta. It is only necessary to keep constantly in mind that in the actual structure the units there schematized are enormously multiplied in numbers and in complexity, and tangled together with no consideration for the microscopist. The total exposed surface area of the villi in a fully formed placenta has been estimated at from 7 sq. m. (Dodds) to 14.7 sq. m. (Dees-Mattingly)—a generous area for fetal-maternal metabolic interchange.

It should be emphasized that at no time during pregnancy is there any mingling of fetal and maternal blood streams. The fetal circulation is, from its first establishment, a closed circuit. With regard to the interchange of materials, the chorionic villi stand in much the same relation to the source of supplies as our own intestinal villi. They are bathed in a medium from which utilizable substances may be absorbed into their blood vessels. But all interchange must in both cases be by diffusion and absorption across the endothelial walls of the blood vessels, and the overlying connective tissue and epithelium. It is not profitable, however, to push such a comparison too far, for in the intestine we are dealing with merely a one-way transfer. In the placenta there is not only the absorption of foods and oxygen from the maternal blood stream, but also the elimination into the maternal blood of carbon dioxide and the nitrogenous waste products of the embryo's metabolism. Stated in another way, the placenta must perform for the embryo the interchanges which in an adult are carried out by the lungs, the gastro-intestinal tract, and the kidneys.

The changes in the endometrium so far dealt with have been presented primarily from the standpoint of trying to make clear the structure and functional significance of the placenta. There remain other characteristic histologic alterations in the decidua, and in the nonplacental embryonic membranes, which can not be passed by without comment. When an embryo is implanted the changes thereby initiated involve the endometrium as a whole, even though only one small area of the endometrium has direct contact with the chorion. Presumably this widespread response is controlled through the action of some hormone arising from the embryo or its membranes. The entire uterine mucosa increases in thickness and vascularity and the deep portions of the glands become tortuous and distended. These early changes seem merely

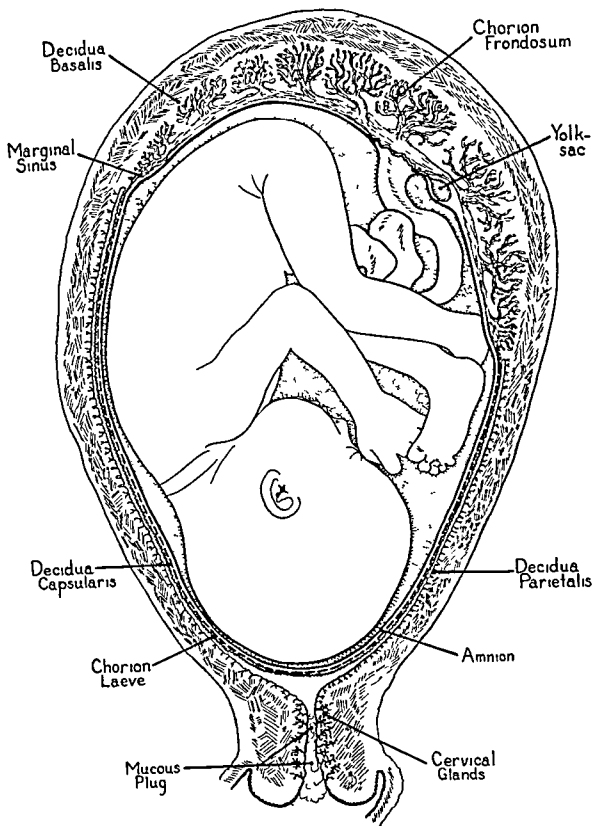


FIG 92 Diagram showing relations to uterus of a five-month fetus and its membranes. Uterine structures have been colored red to contrast with fetal structures, shown in black and white. Amnion is drawn as a solid black line, amniotic cavity is supplied, and chorion laeve is represented by a broken line.

Becoming increasingly conspicuous in microscopic sections of the placenta during the latter part of pregnancy is a peculiar acidophile substance known as *fibrinoid*. This material seems to be a ground substance formed from the



FIG 91 Decidua parietalis A, Section through entire thickness of parietal mucosa from a uterus containing a 16.5 mm embryo (Photomicrograph, $\times 20$, loaned by Dr. George W. Bartelmez.) B, Moderately magnified ($\times 116$) section from mucosa of a uterus containing a 33 mm embryo (University of Michigan Coll., EH 47.) C, A few decidua cells more highly magnified ($\times 450$), from a uterus in the fourteenth week of pregnancy (Preparation loaned by Dr. Burton L. Baker.)

uterine mucosa and chorionic tissue in combination with fibrinous material probably derived from the maternal blood. Fibrinoid tends to be deposited in three rather characteristic regions (1) In the chorionic plate, (2) in tissue

usually reveal physical indications of pregnancy by the sixth week after fertilization, that is, about when the second missed menstrual period would have been expected (Fig 105)

Once the placenta is well established, the growth of the embryo becomes exceedingly rapid. The diagrams reproduced as Fig 93 indicate the changes in the size and position of the uterus as pregnancy advances. The outlines of the uterus can be palpated at progressively higher levels in the abdomen until about the middle of the last month of pregnancy. Usually about 10 days before delivery is expected there is a tendency for the uterus to settle deeper into the pelvis. Fig 94 shows the relations of the uterus to other pelvic structures during labor.

Birth and the "After-birth" The placental attachment normally occurs relatively high up in the body of the uterus. This results in the much thinned decidua capsularis, the chorion laeve, and the adherent amnion, which together form one composite fibrous membrane, being the only structures lying over the cervical outlet (Fig 92). With the beginning of the muscular contractions which mark the onset of labor, the amniotic fluid is squeezed into this thin part of the chorionic sac and the sac acts as a preliminary dilator of the cervical canal (Fig 94). As the periodic contractions become more frequent and more powerful, the investing membranes rupture at this region, freeing the embryo from its fetal envelopes but leaving the placenta still attached within the uterus. This retention of the placenta is of vital importance, for the process of birth ordinarily extends over several hours, and were the fetus to be prematurely cut off from its uterine associations it could not survive the resulting interruption of its oxygen supply.

Continued uterine contractions, aided by voluntary contractions of the abdominal muscles, force the fetus into the slowly enlarging cervical canal until it is dilated sufficiently to permit the fetus to begin to move out of the uterus. When this has been accomplished, the obstetrician speaks of the first stage of labor as having been passed. The second stage of labor is much briefer than the first. Once the fetus passes the cervical canal it moves promptly through the vagina to "present itself" at the perineum. Dilation of the vulval orifice of the vagina progresses much more rapidly than did dilation of the cervix, and once the presenting part of the body—usually the head—passes this outlet, the rest of the body emerges rapidly. With the tying off and cutting of the umbilical cord the relations with uterus and placenta are ended and the newborn infant is for the first time an independently living individual.

In the usual course of events, it is some 15 or 20 minutes after the delivery of the fetus that the uterus begins again to go into a series of contractions which loosen the placenta and the decidua from its walls and finally expel them. Associated with the placenta are the torn remnants of the ruptured *amnion* and *chorion laeve*, and the umbilical cord. This entire mass constitutes the so-called after-birth (Fig 95). The placental portion of the after-birth is a rounded disk averaging from 15 to 20 cm. in diameter. Except at the margins it is some 2.5 cm. in thickness and may weigh anywhere from 500 to 1000 Gm.

bordering the intervillous spaces, and (3) in a zone deeper in the decidua basalis. As long as it remains moderate in amount, fibrinoid is to be regarded as merely a by-product of the readjusting of fetal and maternal tissues in their changing interrelations. Under certain pathological conditions, the fibrinoid may become sufficiently abundant to interfere with the free metabolic interchanges between the fetal and maternal parts of the placenta.

Growth of Uterus During Pregnancy Striking histological changes in the uterus begin, as we have seen, promptly after the implantation of the embryo. A considerable period elapses, however, before the growth of the uterus is sufficient so that its size increase can be detected by physical examination.

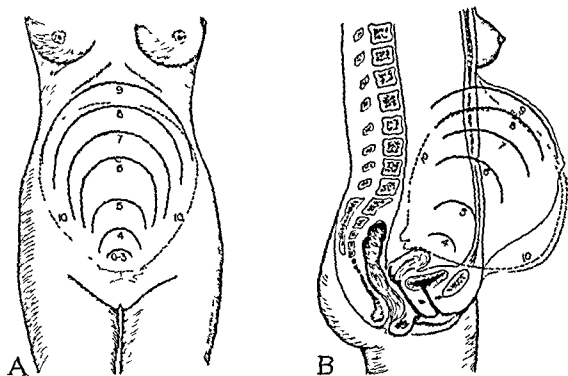


FIG. 93. Diagrams showing changes in size and position of uterus during pregnancy. Numbers indicate "menstrual age" in lunar months. A, Ventral view (Modified from Broman). B, Lateral view (Modified from Eufinger).

This seems but natural if one stops to consider the fact that no extensive growth of the embryo can occur until the elaborate placental mechanism is sufficiently well established to permit the embryo to draw freely on the maternal blood stream for its metabolic needs. A full month after fertilization the embryo is only about 4 to 5 mm. in length and its entire chorionic vesicle is only 15 to 20 mm. in diameter (Fig. 53, lower right). Even at five weeks, the embryo itself is less than a third of an inch in length, and the chorionic vesicle is only about an inch in diameter (Fig. 85, B). Increased vascularity of the uterus has, however, by this time supplemented the increase in its size due to the contained embryo. In another week there is, also, a striking softening of the upper cervical portion of the uterus as compared with its state in a non-pregnant woman (Hegar's sign). Taking into account the cervical changes as well as the increase in the size of the uterus, a skillful pelvic examination will

In general, a normal placenta is about one-seventh of the weight of the fetus with which it is associated (Potter and Adair, 1940, p 95) On its maternal face can be seen the cotyledonary areas with more or less ragged-looking sulci

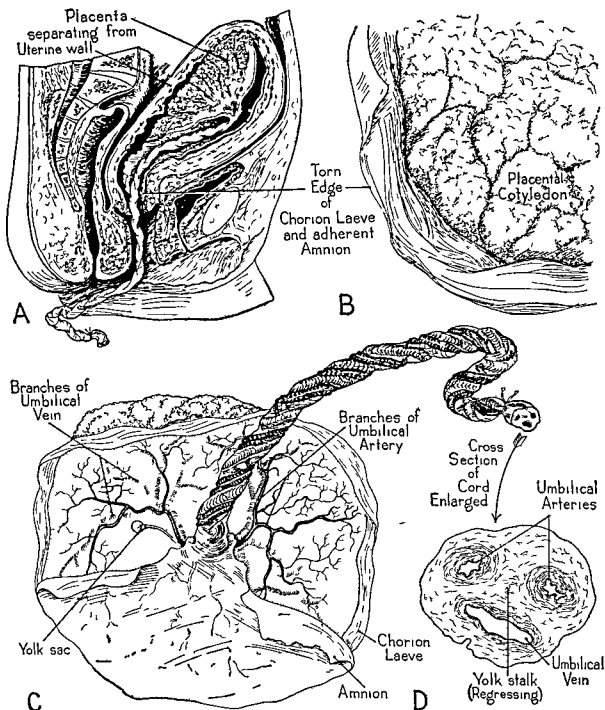


FIG 95 Placenta and umbilical cord at term A, Separation of placenta from uterine wall (Dickinson-Belski) B, Quadrant of uterine face of detached placenta C, Fetal face of placenta (Modified from Corning) D, Cross-section of umbilical cord ($\times 3$)

between them marking the locations where the placental septa were pulled loose (cf Figs 89, 95, B)

The fetal surface of the placenta is covered by the smooth, glistening amnion, through which can be seen the radiating branches of the main ves-

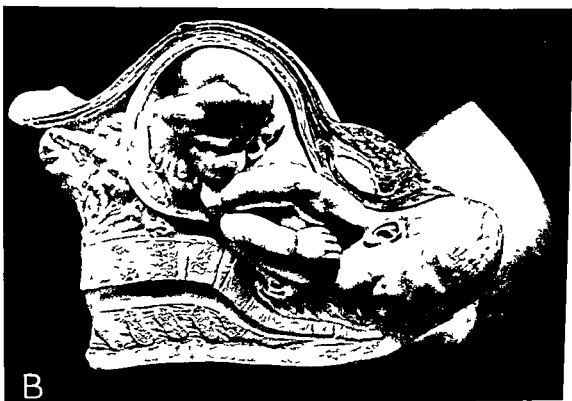


FIG 94 Models showing process of birth (From the Dickinson Belski series done for the Maternity Center Association) A, Head passing through dilated cervix into upper part of vagina. Membranes have remained unruptured unusually long B, Presentation of head at perineum

from her nonpregnant cycle are the cessation of ovulation and the suppression of menstruation. This suggests at once that the corpus luteum must in some manner be involved, for in the cycle of a nongravid individual the hormone (progesterone) from the corpus luteum of ovulation appears to be responsible both for the temporary inhibition of the development of the next crop of ovarian follicles, and for the premenstrual changes in the endometrium. In the nonpregnant woman, both of these physiological effects diminish about 14 days after the liberation of the ovum, at the time when the corpus luteum of ovulation begins to show histological signs of involution and a diminished hormone output. At this time the constructive phase of the uterine cycle ends and the hypertrophied endometrium is sloughed off in the ensuing menstruation. Coincidentally in the ovary, once the inhibiting effect of the corpus luteum hormone is removed, a new crop of follicles begins to enlarge under the influence of the follicle-stimulating hormone of the anterior lobe of the hypophysis (Figs 24, 29).

If, however, fertilization occurs and the implantation of an embryo follows, the picture changes abruptly. As we have seen, the young embryo embeds itself at the time when the endometrium is in its active secretory (premenstrual) state. If implantation takes place, the menstrual period which was impending fails to occur. Instead of undergoing abrupt regressive changes, the endometrium continues to develop in the direction it was going in the premenstrual stage, and its increased glandular activity and increased vascularity are capitalized by the newly implanted embryo.

The initial phase of the mechanism which brings all this about we know at present largely by inference. There must be some hormone, probably originating from the chorionic vesicle, which affects the corpus luteum. For, if the nidation of a young embryo occurs, the subsequent history of the corpus luteum is changed, and instead of beginning to undergo involution about two weeks after it started to form from a ruptured follicle, the corpus luteum continues its growth and secretory activity. During the first three or four months of gestation it grows to a size several times as large as a corpus luteum of ovulation (Fig 16). Even when, in the last half of gestation, it shows indications of involution, the regressive changes are slow and the corpus luteum of pregnancy remains recognizable on gross examination of an ovary for some time after delivery.

There is every reason to believe that the corpus luteum of pregnancy continues to produce the same kind of hormone which it did as a corpus luteum of ovulation before it was activated to increased growth and a longer period of activity. Thus it would appear that the same hormone which in a nongravid individual delays the formation of new ovarian follicles until a period of rest has been enforced acts in a gravid individual to inhibit ovulation until pregnancy is completed and the reproductive mechanism is ready to commence again its cycles of preparation for another pregnancy. There is considerable evidence to indicate that in the last half of gestation this hormone is produced also in the placenta, supplementing the ovarian source.

sels which connected the placenta with the fetus by way of the umbilical cord. Extending peripherally beyond the placenta are the torn membranes which were ruptured in the first stage of labor, before the fetus passed through the cervix of the uterus. As has been pointed out, this membranous portion of the fetal envelopes consists of amnion, chorion laeve, any remnants there may be of the decidua capsularis, and adherent shreds of the decidua parietalis stripped off at the line of cleavage formed by the stretched uterine glands. Naturally, the abrupt shedding of such extensive masses of tissue from the uterus involves some hemorrhage. This is, however, ordinarily surprisingly small in amount when one considers the size of the denuded areas. Following the expulsion of the after-birth, the uterus contracts firmly, lessening the rate of blood flow by compression and thereby facilitating the coagulation which gradually closes the ruptured vessels.

Then follows a period of repair of the uterine lining similar to that after menstruation. With the more radical denuding of the uterine lining which follows delivery, postpartum reconstruction naturally takes longer than post-menstrual repair. Some oozing of blood or blood-tinged serum (the "lochia") may be expected to continue for from two to four weeks. After the raw surface of the endometrium is repaired, its growth-secretory phase is slow to reappear and, even in women who do not nurse their babies, it is ordinarily about three months after parturition before menstruation again occurs. Nursing further delays the re-establishing of the menstrual cycle, but ovulation may be resumed and another pregnancy ensue before menstruation recurs.

Regression of Cord Stump The manner in which the fetal stump of the umbilical cord changes in appearance postnatally may be a matter of importance if a medicolegal question arises as to how long an infant survived following birth. Potter and Adair (1940) give the following summary of the changes during the first week: for the first 24 hours the cord is shrunken and bluish but still soft, during the second and third days it becomes brownish and dry, in the fourth and fifth days it becomes darker brown, more twisted, and takes on a curious semitranslucent appearance, separation of the shriveled stump from the umbilicus usually occurs on the seventh day.

HORMONAL REGULATORY ACTIONS DURING PREGNANCY

We have already considered some of the hormonal factors controlling the cyclical changes occurring in the reproductive organs of the nongravid female. The same or similar hormones are present in the system during pregnancy, but once the embryo is established in the uterus new and modifying factors become operative. Our knowledge of these hormone interactions during pregnancy is very recent and still far from complete. It is, however, a field of such intriguing biological interest and of such clinical importance that one must be familiar at least with the direction in which current investigations seem to be pointing.

When a woman becomes pregnant, two of the most striking departures

the activity of the placenta in producing the same or similarly acting substances. The exact nature of the mechanism is not known, but the clinically important fact that removal of the ovaries in the latter part of pregnancy does not result in abortion is well established. It is presumed that this change from

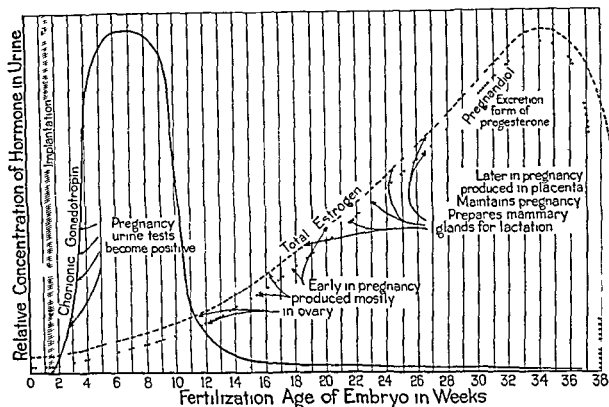


FIG 96 Graph indicating empirically the change in excretion rate of certain hormones during pregnancy (Schematized from a number of sources)

the situation in early pregnancy is due to maintenance of adequate hormone levels through placental activity in spite of the removal of the ovarian source

ANOMALIES OF FETAL-MATERNAL RELATIONS

Anomalies of Placental Shape As we have seen, the disk shape which is ordinarily exhibited by the full-term human placenta develops gradually through the regression of the chorionic villi and the decidua where their relations are unfavorable, and by the maximal development of villi in the most favorable area. In general, in such opportunistic processes there is likely to be considerable variation from the standard pattern. The placenta may exhibit a bilobed shape (Fig 97, A), it may be two disks instead of one (Fig 97, B), or it may be in the form of one main disk with one or more small accessory disks (Fig 97, C). None of these variations is of any particular functional significance to the embryo, provided the placental tissue is healthy and the chorio-uterine vascular relations are normal. It is, however, important to know that such conditions may occur, for if any placental tissue remains in the uterus after the expulsion of the after-birth, postpartum hemorrhage is likely to continue. The careful obstetrician, therefore, inspects the after-birth to make sure of its completeness. In the event of there being a small accessory

The corpus luteum hormone has an effect on the pregnant uterus qualitatively similar to that which it exercises on the nonpregnant uterus. In the cyclic changes which occur in the absence of pregnancy, we found the corpus luteum hormone acting in conjunction with the estrogenic hormone to bring about the characteristic premenstrual development of the endometrium (Fig. 29). It was pointed out, also, that the menstruation which followed was the expression of the abrupt cessation of the preparatory changes, and the casting out of the fruitlessly constructed nesting place for the embryo. If, during the proper phase of one of these patiently repeated preparatory cycles, an embryo arrives and takes possession of its partially prepared domain, a hormonal messenger is promptly sent to the corpus luteum to continue constructive operations. Speaking figuratively—the corpus luteum responds by enlarging its plant and increasing production. This is just another way of saying what we already know—that a corpus luteum of menstruation becomes transformed into a corpus luteum of pregnancy. With the constructive phase of the uterine changes pushed by the continuing drive of corpus luteum hormone, the regressive phase—that is to say, menstruation—does not occur.

Emphasis has already been laid on the tremendously rapid growth of the trophoblast which follows implantation. Although the chain of evidence is not complete, it seems probable that the growing trophoblast is the source of the hormone mentioned in the preceding paragraph as acting on the corpus luteum and causing it to continue its growth. There is in the urine of pregnant individuals a substance known as chorionic gonadotropin which is probably a degradation product of the hormone in question. As the trophoblast of the newly implanted chorionic vesicle grows, there is an abrupt rise in the excretion of chorionic gonadotropin (Fig. 96). It is this rise that is taken advantage of in the urine tests for pregnancy. These tests depend on the capacity of this material to stimulate the ovaries of rodents. In the Aschheim-Zondek test immature rats or mice are employed. After the animals have been injected with the urine being tested, three critical changes are watched for as indicating a positive reaction: (1) Growth of ovarian follicles, (2) bleeding into the antra of follicles, and (3) the appearance of corpora lutea. In the Friedman test, estrous rabbits are used and the positive reaction watched for is the induction of ovulation.

In addition to chorionic gonadotropin, two other substances which may be recovered from the urine during pregnancy are of special interest. One of these, called pregnandiol, is a degradation product of the corpus luteum hormone progesterone. The other is a complex of the excreted forms of the estrogenic hormone. Both of these substances appear in the urine in relatively low amounts early in pregnancy and rise as pregnancy advances, reaching a peak at about eight months and then dropping abruptly as term approaches (Fig. 96). The hormones which they represent are responsible for the maintenance of effective chorio-uterine relations. If the ovaries are removed early in pregnancy, the resultant hormone deficiency causes abortion to occur. Later in pregnancy, ovarian hormone production appears to be supplemented by

the activity of the placenta in producing the same or similarly acting substances. The exact nature of the mechanism is not known, but the clinically important fact that removal of the ovaries in the latter part of pregnancy does not result in abortion is well established. It is presumed that this change from

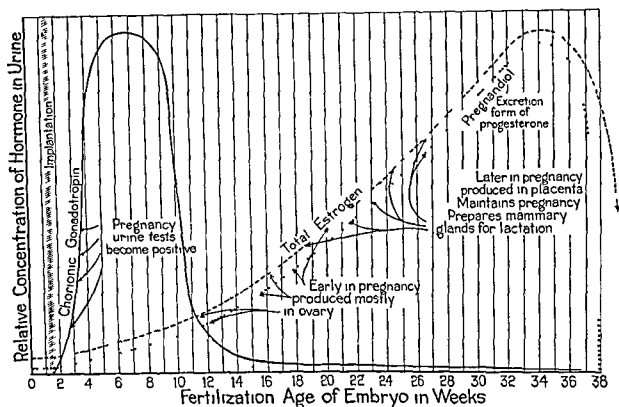


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lobe that failed to come away with the main placenta, the broken vessels which connected it with the main part of the placenta and the umbilical cord can readily be recognized and the appropriate steps taken to free the uterus completely of placental tissue.

Abnormalities of Chorionic Villi More serious than variations in the shape or lobulation of the placenta are abnormalities of the chorionic villi. There occurs—fortunately very rarely—a condition called *hydatidiform mole*

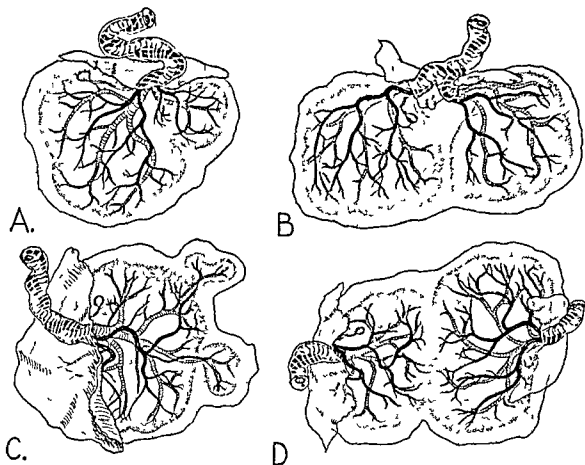


FIG 97 Semischematic diagrams of various types of placenta (Adapted from several sources) A, Partially separate lobes B, Completely separated lobes (Note the single umbilical cord, this is the placenta of a single fetus—not twins) C, Small accessory placental lobes (placenta succenturiata) D, Partial secondary fusion of the originally separate placentae of dizygular twins

in which the villi show degenerative changes accompanied by the accumulation of fluid, so that the branches of the villi become chains of vesicles of varying sizes (Fig 98). The cause of this degenerative change is not known, but its effect on the embryo is obvious. With its means of securing nutrition thus disturbed, the embryo dies and degenerates and abortion of the pathological chorion follows. Such cases must be very carefully watched to make certain that none of the chorionic fragments remain embedded in the uterus.

During the early phases of pregnancy, the chorionic villi are, as we have seen, active in invading the endometrium. Apparently it is quite normal for some of the trophoblast cells at this stage to break away from the villi and be

carried to other parts of the body by the maternal lymphatic stream. This phenomenon is known as *chorial invasion*. The wandering trophoblast cells seem to live for a time insinuated among the cells of the maternal organism and then to die and disappear without causing any untoward disturbance. In rare instances, as is the case with other tissues of the body, chorionic epithelial cells may become malignantly invasive. When this occurs they give rise to a neoplastic growth known as a *chorio-epithelioma*. Such a growth has the same serious implications as cancers arising from other types of epi-

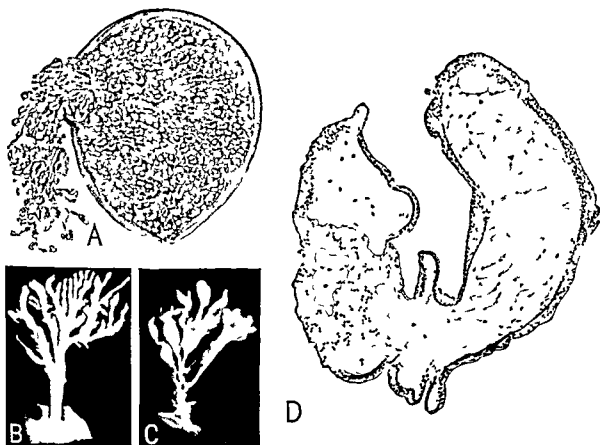


FIG 98 Hydatidiform mole. A, Uterus filled with chorion which has undergone extreme hydatidiform degeneration (From Stander "Williams' Obstetrics," courtesy, D Appleton-Century Co.) B, Normal chorionic villus (After Hertig and Edmonds, Arch Path, Vol 30, 1940.) C, Early hydatidiform change in chorionic villi (After Hertig and Edmonds, loc cit.) D, Section of villus with early hydatidiform degeneration (From DeLee "Obstetrics")

thelial cells. It seems to be rarely, if ever, a sequel to the chorial invasion of a normal pregnancy. In so far as its origin is known it appears to be more likely to occur following abnormal postpartum retention of chorionic tissue, and then only in the occasional case. Retained fragments of the already abnormal villi of a hydatidiform mole are particularly suspect in connection with the origin of chorio-epitheliomata.

Abnormal Sites of Implantation In view of the elaborate preparation of the endometrium to receive and implant a young embryo, the manner in which embryos sometimes become implanted in abnormal locations not so prepared is rather surprising. The attachment and growth of an embryo in

any location other than the uterus is called an ectopic pregnancy. It has been estimated that approximately one pregnancy in 300 starts thus in an abnormal location.² The sites which may be involved are the ovary, the abdominal cavity, or the uterine tubes (Figs 99, 100).

OVARIAN PREGNANCIES (Fig 99, A) These are exceedingly rare and little is known as to just how they arise. One possibility is that a follicle may sometimes rupture without the ovum being liberated from the cumulus. If this occurred it would be possible for spermia to enter the follicle at the point of its rupture and fertilize the ovum while it is actually attached within the ovary. Some such occurrence as this is probably the only one which should be regarded as a true ovarian pregnancy. Another possibility would be that the liberated ovum failed to enter the tube but remained in the peritoneal cavity adjacent to the ovary. If it was fertilized there and developed an active trophoblast layer it could conceivably attach itself to the surface of the ovary, just as it might to the surface of any other conveniently located organ. Strictly speaking such a case should be regarded as an abdominal pregnancy in which the ovary happened to be the abdominal organ which provided the conveniently located vascular surface.

ABDOMINAL PREGNANCIES Abdominal pregnancies are somewhat less uncommon than ovarian, but they are still very rare occurrences. A primary abdominal pregnancy is a possible result when an ovum fails to be picked up by the uterine tubes and thus remains free in the abdominal cavity. It may then be fertilized by spermia which have made their way through the tube, and implant itself on the moist vascular surface of the viscera or mesenteries. Apparently not all abdominal pregnancies arise in this direct manner. They may sometimes be secondary to a tubal pregnancy in the course of which the chorion has ruptured the wall of the uterine tube and then implanted itself again in some part of the abdomen. The older medical literature—of the days when abdominal surgery was undertaken only as a last desperate hope—reports many well-authenticated cases of abdominal pregnancies in which the embryo went to several months' gestation before causing the death of the mother by placental perforation of the viscera or by the intra-abdominal hemorrhage incident to trophoblastic invasion. There are even occasional cases on record of abdominal pregnancies in which a viable fetus was removed by laparotomy. Under present-day conditions, when surgical opening of the abdomen involves a minimal risk, failure to make an early diagnosis and carry out prompt operative intervention would be regarded as inexcusable, and one is increasingly unlikely to see any advanced cases of abdominal pregnancy.

TUBAL PREGNANCY By far the most common location for an ectopic pregnancy is the uterine tube. The ampullar part of the tube is the usual site, about four out of five tubal pregnancies occurring at this level. Anything

² This ratio is quite probably rather high, being based on hospital records where the proportion of cases referred because they presented some complication would be greater than in the community at large. Irving is inclined to believe that in general practice the ratio should be nearer one to 500.

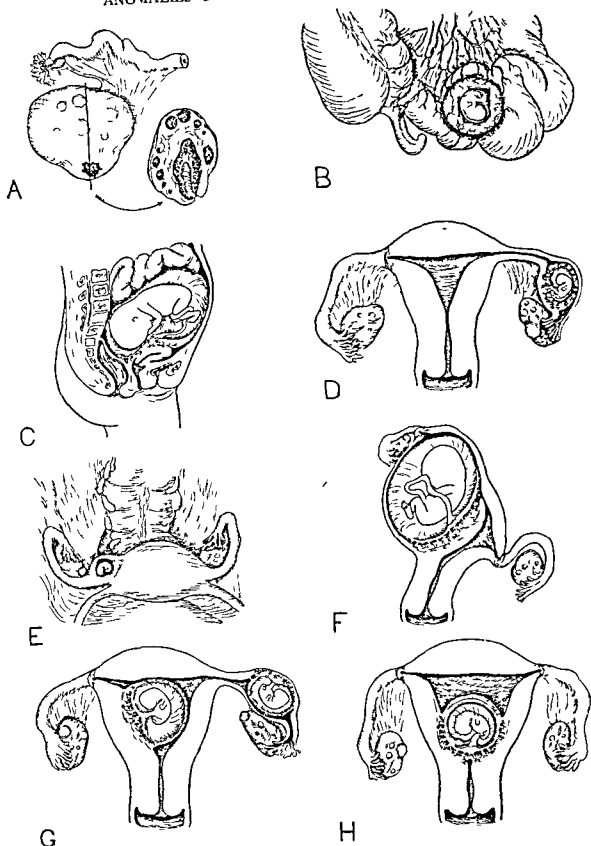


FIG 99 Abnormal sites of implantation of embryo

A Young chorion implanted within a ruptured ovarian follicle. In this particular specimen the embryo was lost by rupture of the chorion (After Mall and Cullen)

B Early abdominal pregnancy (Schematized from a case reported by Schurmann) Chorion was implanted on serosal surface of small intestine

C Abdominal pregnancy (Modified from Cullen) This embryo is much older than that shown in B in this instance site of implantation was in utero-rectal pouch

D Tubal pregnancy in ampullar region. This is the commonest site of ectopic pregnancies (Cf Fig 100 for further detail on the relations in such a case)

E Tubal pregnancy in isthmic region (Schematized after Williams Obstetrics)

F Interstitial pregnancy, i.e. implantation in the part of the tubal lumen surrounded by uterine tissue (Schematized from a case reported by Falls)

G Simultaneous normal intra uterine and tubal ectopic pregnancy (Schematized from a case reported by Falls)

H Schematic diagram showing the early chorionic relations in a case which would develop into a placenta praevia

which impeded the normal migration of the ovum through the tube toward the uterus could be an etiological factor. It is believed that inflammatory conditions of the tubes, arising as a result of gonorrheal or other infections, are most frequently responsible. Certainly the scar tissue formed following a salpingitis causes adhesions of the folds of the mucous membrane, thus creating many blind pockets in which the ovum could become lodged. Congenital malformations of the uterine tube in which the lumen is irregular or beset with diverticulæ probably account for other cases. It is conceivable, also, that even in an anatomically normal tube endocrine disturbances might interfere with the heightened tubal activity which normally occurs following ovulation, and thereby reduce physiologically the efficiency of the mechanism of transporting the ovum.

Whatever the causative factors may be, if the young embryo is delayed in the tube until it begins to form chorionic villi, it will implant itself. For a brief time development is likely to proceed fairly normally. As soon, however, as growth begins to be extensive, complications follow, for the rapidly expanding chorion tends to cause hemorrhage from the walls of the tube. If the bleeding is slow, coagulation may keep pace with it and the chorion be surrounded gradually by an organized clot (Fig. 100). If the areas of the chorion thus separated from the maternal tissues are small, disturbance of the growth of the embryo may be the only immediate result. If these areas become extensive, however, the embryo dies, and when the mass is finally removed at operation one may find that the embryo has been resorbed and the specimen consists of only an empty chorionic vesicle embedded in a massive blood clot.

If, as frequently happens, the invading chorion causes rapid bleeding from the tubal walls, the blood will back through the tube into the abdominal cavity, producing acute symptoms which call for immediate surgical intervention. A similar clinical picture results if the chorion eats its way completely through the walls of the tube. In such cases of ruptured tubal pregnancies, the intraperitoneal hemorrhage is likely to be profuse, and the urgency for its immediate surgical control extreme.

PLACENTA PRAEVIA Extra-uterine sites of implantation such as those just mentioned are not the only ones which may cause difficulties. If the embryo is implanted in the uterus close to the cervical outlet, the placenta is formed in such a position that the fetus can not be delivered until after the placenta has been detached or ruptured. Such a condition is known as placenta praevia. The dangers of such a situation, to the mother from hemorrhage, and to the fetus from asphyxiation, are obvious. Fortunately, irritation of the cervix by the growing chorion causes early abortion in a considerable proportion of cases of placenta praevia. Even if the irritation of the uterus is not sufficient to cause abortion, it may at least give warning of the situation by loosening a small area of the placenta and causing hemorrhage. When such cases go to full term they constitute a real challenge to the skill and resourcefulness of the obstetrician.

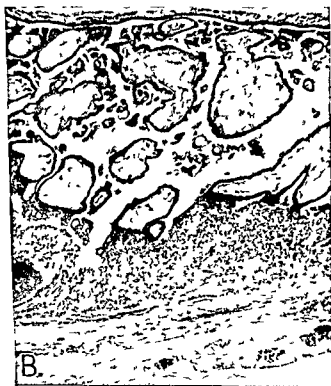
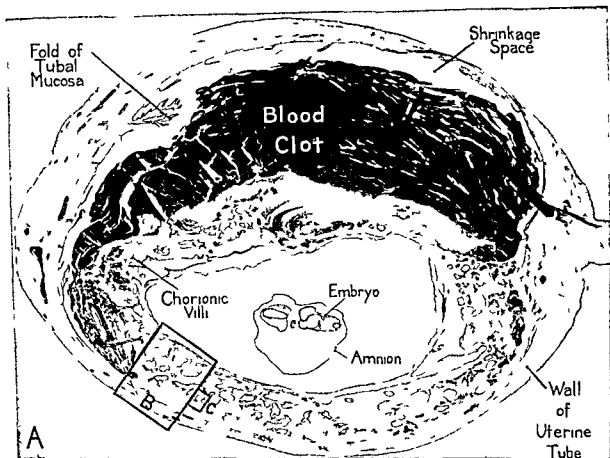


FIG 100 Tubal pregnancy with embryo of about one month, fertilization age (University of Michigan Coll, EH 265, specimen acquired through courtesy of Dr C V Weller) A, Low-power photomicrograph of a cross-section of the entire uterine tube with embryo in situ B, Moderately magnified area of tubal wall and the implanted chorion at location indicated in A C, Chorionic villus ($\times 135$) at point of its attachment (area indicated by the small rectangle marked "C" in A)

Abnormalities of Amnion The most common departures from the normal occurring in connection with the amnion involve the amount of amniotic fluid. The usual amount present in the late stages of pregnancy is just sufficient to keep the fetus free within its membranes—somewhere in the neighborhood of 1000 to 1500 cc. A condition in which the amniotic fluid is excessive—say over 2000 cc—is termed polyhydramnios. A deficient volume—less than 500 cc—is termed oligohydramnios. Low volume, with the danger of its leading to adhesions, is apparently more serious than an excess of fluid. It has long been believed that adhering amniotic bands were the primary causative factors in the intra-uterine amputations with which they are known to be associated. But, as Streeter has pointed out, one should not be too ready to attribute such damage solely to the simple mechanical factor of the amount of fluid present. It is possible that the adhesions are not causal, but are the result of local degenerative changes in the fetal tissues. On this interpretation, adhesions to the amnion would form where the protective epithelial covering of the fetal integument was damaged, and where fetal and amniotic fibrous connective tissues came in contact.

Superfetation Under ordinary circumstances, once pregnancy is established, no additional conception can occur until after the current pregnancy has been terminated. This is doubly insured by the cessation of ovulation during pregnancy and by the occlusion of the cervical canal of the gravid uterus by a plug of tenacious mucoid material produced by the cervical glands. A few cases have, however, been reported which appear to be exceptions to this general rule. Instances have apparently occurred in which a markedly younger fetus has been delivered along with a full-term infant. A startling variant of the same situation is the report of a case in which a younger fetus is said to have remained in the uterus during the birth of its older womb-mate, and to have been born alive some weeks later when it, in its turn, had reached full term. Such cases, explicable only on the assumption that fertilization and implantation can sometimes occur following an unsuppressed ovulatory cycle subsequent to the beginning of pregnancy, are known as instances of superfetation. The extreme rarity of such an occurrence can not be too strongly emphasized, especially since some of the alleged cases could be more plausibly interpreted as twins, one of which failed to keep pace with the growth of the other. Such unequal growth of litter-mates in animals producing several young at a birth is quite familiar to animal breeders, who have given us the expressive term "runt" for the embryo which was ill-favored in its intra-uterine environment and lagged behind its mates in development. An authentic case of superfetation is to be regarded as a sort of medical curiosity in which all of the mechanisms which ordinarily prevent such an occurrence have for some unknown reason broken down simultaneously.

Age, Growth, and Changes in External Form of Body

ESTIMATION OF AGE AND METHODS OF MEASURING EMBRYOS

Fertilization Age Although, in a sense, an embryo pre-exists in the gametes from which it arises, its life as a new individual must be regarded as commencing at the moment of fertilization. The fertilization age of a human embryo which comes into the laboratory for study is practically never known except as a rough approximation. Even when such specimens are accompanied by unusually complete clinical data, this information usually is based on nothing more reliable than the patient's attempts to cudgel her memory into fixing the time of events some weeks in the past. Supposing the date of onset of the last menstrual period which occurred was marked on a calendar, there is still the uncertainty as to where in her menstrual cycle the particular woman in question ovulated. If, for the sake of argument, we assume that the time of ovulation and of a single coitus which must have been the fruitful one were known, even this would place the time of fertilization only within some 12 to 24 hours. If an embryo with such an unusually circumstantial history were recovered as the result of a spontaneous abortion, there would still be uncertainty at the other end of its life history. We would have no means of knowing how long before extrusion its normal growth had ceased and death had ensued. Judging from the amount of resorption of the embryonic body which is sometimes seen in aborted chorionic vesicles, it would seem quite apparent that this interval between embryonic death and abortion may be considerable. It is certainly too highly variable to permit more than a tentative assessment of its duration in any individual case. Our best-preserved embryos come from surgical cases, and when a normally growing embryo is removed at operation we have at least a definite end-point in its life history.

All this serves to emphasize the special importance of securing the best possible history in any case where a pregnancy must be terminated surgically, and then seeing that this history, together with the carefully preserved embryo, goes to a laboratory where the specimen will be properly measured and then studied by other means suitable for determining the degree of its developmental progress. It is only from the study of accumulated data of this sort that

we can increase the accuracy of our knowledge of the timing of critical events in intra-uterine life

Methods of Measuring Embryos It is self-evident that to be of any value for comparisons, measurements of embryos must be made according to standard methods. Various base-points have been used by different workers, but

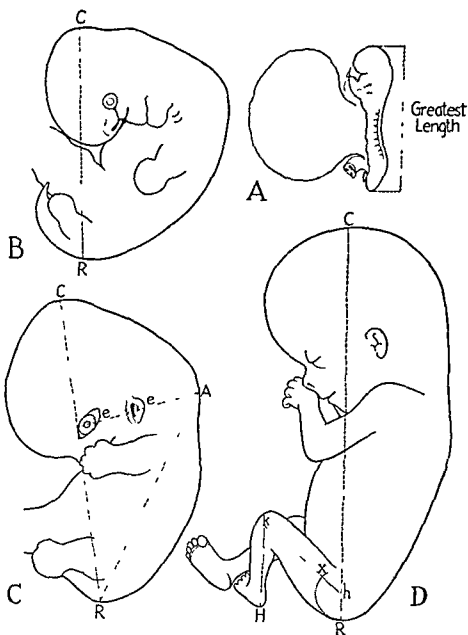


FIG 101 Diagrams showing methods of measuring embryos (After Mall) For explanation of the different measurements indicated by the letters see text

gradually the measurements indicated in Fig 101 have come to be quite generally adopted. For a very young embryo having a body which is still fairly straight, "the greatest length" (Fig 101, A) is the most simple and useful measurement. As one would expect, however, there is considerable individual variability as to size in different embryos of the same age, and in

attempting to determine the degree of developmental advancement of young specimens a somite count should be used in addition to measurements (See the following table)

TABLE SHOWING APPROXIMATE TIMES OF APPEARANCE OF SOMITES

<i>Day</i>	<i>Somites</i>	<i>Day</i>	<i>Somites</i>
17	1-3	25	24-26
18	3-5	26	27-28
19	6-8	27	29-30
20	9-11	28	30-31
21	12-14	29	32-33
22	15-17	30	34-35
23	18-20	31	36-37
24	21-23	32	38-39

The information on the basis of which the ages of human embryos are estimated is still fragmentary and unsatisfactory. The above table must be regarded as a tentative approximation, subject to revision as more complete data becomes available.

As embryos begin to exhibit a marked curvature of the body, it becomes impractical to make any direct measurement that approximates their total body length. During this period, the most commonly employed dimension is the crown-rump length, or "sitting height," ordinarily abbreviated as C-R (Fig 101, B).

The crown-rump measurement continues to be of use in describing older embryos, but as the body becomes more highly differentiated additional measurements become of increasing value. The "spine-length" is a measurement occasionally used in detailed descriptive studies. It is especially valuable in dealing with embryos between 6 and 10 weeks because it helps to show up variations in crown-rump dimensions which are due to differences in the degree of cervical flexion caused by extrinsic factors such as distortion during fixation. In making this measurement, a line is projected backward through the center of the eye and the ear. This line passes approximately through the level of the joint between the atlas and the skull. Taking the point where such a line comes to the dorsal surface of the body at the cervical flexure, therefore, gives for all practical purposes a point ("A" in Fig 101, C) which corresponds with the cephalic end of the spinal column. The distance from this point to the rump constitutes an embryo's spinal length, or A-R dimension.

Particularly useful in the older stages of development is the C-H, or crown-heel dimension. This is the "standing height" of the embryo and is, therefore, much more readily comparable with the usual measurements taken post-natally. The arc of a circle, described about the hip joint as a center, with such radius that it coincides with the curvature of the rump, indicates that portion of the leg length (x-k-H in Fig 101, D) which must be added to the sitting height (C-R) in order to obtain the standing height (C-H).

GROWTH OF BODY AS A WHOLE

Using the measurements from the best-preserved embryos with the most complete and seemingly most dependable clinical histories, it is possible to

construct tables and graphs which are exceedingly useful in assessing the age of the many embryos not accompanied by clinical histories. As a matter of fact, the study of an embryo's morphology and the utilization of age-length graphs based on data accumulated over many years, and rechecked repeatedly

DATA ON GROWTH BY WEEKS (FERTILIZATION AGE)

<i>Age in Weeks</i>	<i>C R Length in Mm</i>	<i>Weekly Length Increase in Mm</i>	<i>Configuration of Body</i>
3	2-3	2	Body axis just beginning to show bending
4	1-5	3	Flexion strongly marked
5	7-8	5	Maximum flexion
6	12-13	7	Cervical flexure about 90°
7	19-20	9	Cervical flexure about 60°
8	28-30	11	Cervical flexure about 30°
9	39-41	12	Cervical flexure about 22°
10	51-53	13	Cervical flexure about 15°
11	64-66	13	Cervical flexure about 8°
12	77-79	14	Neck almost straight
13	91-93	14	
14	105-107	14	Dorsal flexure
15	119-121	13	becomes more marked
16	132-134	13	and
17	±147	13	whole body
18	±160	13	is curved into
19	±173	12	C shape
20	±185	12	C-II measurement
21	±197	11	and
22	±208	11	body weight become
23	±219	11	better criteria of growth rate
24	±230	10	than C-R
28	±270	10	
32	±310	9	
36	±346	8	
38	±362		

in the light of advances in our knowledge, will yield more trustworthy information as to the age of an embryo than can possibly be gleaned from anything except an unusually complete and accurate clinical history. It should be emphasized that this matter of embryonic size and age is of practical as well as theoretical importance. The age of an aborted embryo is always of interest to the patient and of significance to the attending physician. In certain medi-

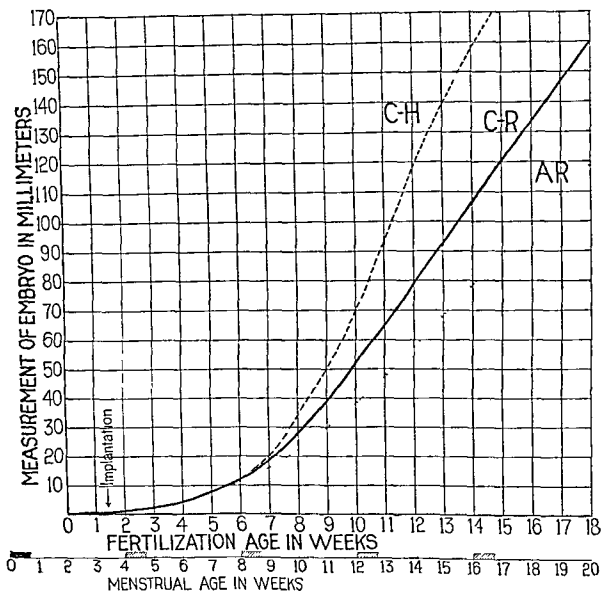


FIG. 102 Smoothed curves showing increase in the commonly used linear dimensions of the body during the first 18 weeks (Adapted from the data of Mall and Streeter and some of the more recently acquired material on younger embryos)

colegical cases, accurate assessment of age from the specimen alone may be a crucial point. Knowledge of the size that an embryo should have attained at any given time after the beginning of pregnancy may be the means of diagnosing intra-uterine death of the fetus, or of making the correct differential diagnosis between a pregnancy and a uterine tumor.

Use of Menstrual History in Formulating Age-length Data A graph covering the age changes in crown-rump length during the period in which

construct tables and graphs which are exceedingly useful in assessing the age of the many embryos not accompanied by clinical histories. As a matter of fact, the study of an embryo's morphology and the utilization of age-length graphs based on data accumulated over many years, and rechecked repeatedly

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3	2-3	2	Body axis just beginning to show bending
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10	51-53	13	Cervical flexure about 15°
11	64-66	13	Cervical flexure about 8°
12	77-79	14	Neck almost straight
13	91-93	14	
14	105-107	14	Dorsal flexure becomes more marked
15	119-121	13	and
16	132-134	13	whole body is curved into C shape
17	± 147	13	C H measurement
18	± 160	13	and
19	± 173	12	body weight become better criteria of growth rate than C R
20	± 185	12	
21	± 197	11	
22	± 208	11	
23	± 219	11	
24	± 230	10	
28	± 270	10	
32	± 310	9	
36	± 346	8	
38	± 362		

within a day or two if it is to occur at all. Analysis of a large group of pregnancies with good clinical histories is confirmatory, indicating that the great majority of conceptions occur from intercourse between the ninth and the nineteenth day of the menstrual cycle, with the statistical peak at about the thirteenth to fourteenth day.

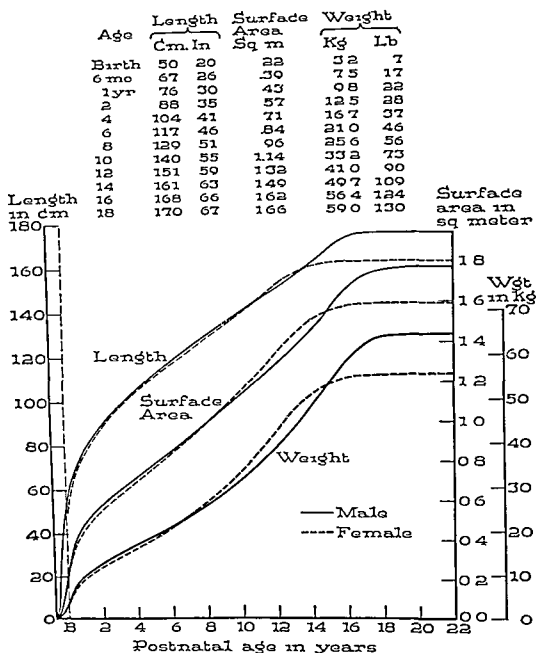


FIG 104 Graphs and tables illustrating growth of the body in length, surface area, and weight during postnatal life. Body-length measurements are crown-heel (After Edith Boyd, from Scammon, in Morris "Human Anatomy.")

In spite of the fact that present knowledge thus clearly shows that the so-called "menstrual age" is not at all the age of the embryo, the use of the menstrual history as a basis for age calculations is nevertheless exceedingly useful provided the necessary corrective factor is introduced. A fairly reliable menstrual history is much more likely to be available than anything approach-

this measurement is most useful is reproduced as Fig 102. It will be noted that this graph is set up on the basis of fertilization age. But since in many similar graphs time is calculated from the first day of the last menstrual period which occurred, a second time line on this basis has been added. The practice of using the last menstruation as a basis for reckoning is due partly to the reten-

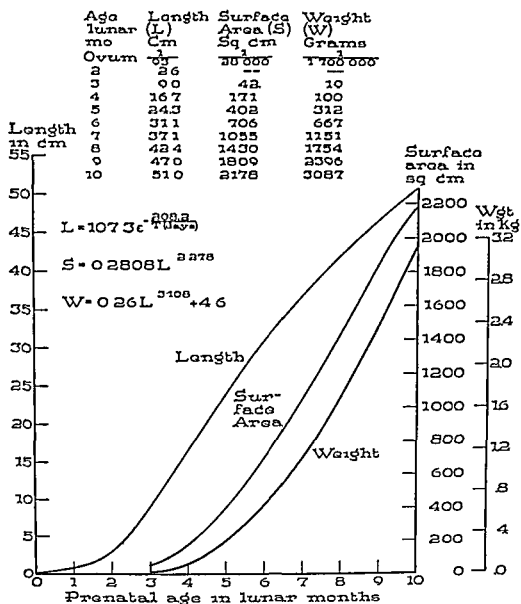


FIG 103 Curves, formulae, and tables illustrating growth of the body in stature (total height or C-H measurement), surface area, and weight during prenatal life (After Edith Boyd, from Scammon, in Morris "Human Anatomy")

tion of an old approach which erroneously assumed that fertilization and implantation were nearly coincident with menstruation. From this viewpoint, we still have retained the expression "the menstrual age" of an embryo. As has been pointed out in Chapter 3, we now know that ovulation occurs approximately midway between menstrual periods, and that, because of the brief period of viability of the unfertilized ovum, fertilization must take place

year-old child which had continued to increase in height at the rate of 1.5 mm a day would be 20 feet tall. Thus it is apparent that even what we are accustomed to think of as the rapid growth characteristic of childhood and adolescence is slow compared with the growth rate in utero.

When one begins to think in terms of weight, the figures become startling. In the 20 years from birth to maturity, the increase in weight is a mere twenty-fold, in the nine months it takes the ovum to grow into a full-term fetus, the increase is about six billion times. Arey has made the arresting calculation that if the body weight continued to increase postnatally at the rate which prevailed in utero, "the weight of the adult would be two millions of millions times that of the earth."

The relation of the body's surface area to its total mass is significant with reference to metabolic rate and the rate of heat loss. Boyd's measurements (Fig. 103) give the surface area at term as about 2200 sq. cm. Inspection of Fig. 104 will show that this area doubles by the end of the first year, triples by the fourth year, and by maturity becomes almost eight times the birth area. Since the adult body weight is about 20 times birth weight, it is evident that, in spite of the absolute increase in surface area, there is a relative loss per unit of body weight. Put in terms of square centimeters of skin per kilogram of body weight, the newborn infant has something over 800 while the adult has less than 300.

DEVELOPMENT OF FORM OF BODY AND CHANGES IN ITS EXTERNAL APPEARANCE

Body Form in Young Embryos The embryonic body at first is so totally different from that of the adult that it becomes a matter of natural interest to know when in the course of intra-uterine life certain familiar features appear. Even for those who think readily in terms of graphs and tables of quantitative data, there are many things about the shape and proportions of the body which are more effectively set forth in simple pictorial form.

Embryos of the first seven weeks have already been depicted with the aid of photomicrographs taken at different magnifications which seemed best suited to show the details of body configuration at each specific stage. It will be recalled that the vaguely organized spheroidal cell mass of the first two weeks becomes molded, early in the third week, into an embryonic disk with the primitive streak as its chief structural feature (Fig. 46). Later in the third week, the embryonic disk becomes reshaped into a more or less cylindroid body in which the head and tail and segmentally arranged somites can be made out, but which still lacks any indication of appendages (Fig. 50). During the fourth week, we saw the originally straight body become markedly flexed (Figs. 51, 52, 53). In the sixth and seventh weeks, the flexure in the cervical region becomes particularly marked, the body axis at this level changing direction through nearly 90 degrees (Figs. 59, 61).

With these figures available for consultation as to details of body struc-

ing a trustworthy ovulatory or coital history. From a practical standpoint, therefore, often the best that can be done is to use a "presumptive fertilization age" arbitrarily calculated on the assumption that fertilization occurred two weeks after the onset of the last menstrual period. Used in conjunction with age-length data of the type assembled in Figs 102 and 103, such an age approximation is reasonably satisfactory in keeping track of the size an embryo can be expected to attain at the various stages of pregnancy.

Use of Menstrual History in Predicting Time of Birth To the discomfort of both the patient and the obstetrician, the day when birth will occur in a particular pregnancy can not be predicted with exactness. Birth occurs on the basis of statistical averages 38 weeks after conception, or 40 weeks after the onset of the last menstrual period which occurred. The usual rule of thumb in predicting the time of confinement is to add a year and a week to the date on which the last period commenced, and then count back three months. There is, however, much variability, and the chief difficulty with all such predictions by date is the illusion of precision which they are likely to create in the mind of the patient. It is much wiser to suggest a two- to three-week time zone within which delivery is likely to occur.

Increase in Height, Weight, and Surface Area During the latter part of pregnancy, the rate of increase in the C-H dimension or standing height, the weight, and the surface area of the fetal body are important, particularly when for any reason it becomes of interest to compare pre- and postnatal growth. The most extensive and accurate material of this type has been assembled by Scammon and Boyd and their co-workers at the University of Minnesota. The data and graphs here utilized are taken mostly from this work. Fig 103 gives a graphic summary of growth rates for intra-uterine life, and Fig 104 covers comparable data for the period of postnatal life during which adult stature is being acquired. Quantitative information of this type is exceedingly useful to have available for ready reference, but length and weight for a large series of specific ages is decidedly not the type of material one would attempt to memorize. Certain general trends might, however, receive a word of comment.

In making a visual comparison of the graphs covering pre- and postnatal growth rates, one not accustomed to dealing with data in this form should perhaps be cautioned against being misled by looking only at the steepness of the rise of the growth curves in the two figures. It must be appreciated that the time scales are different, the growth during the fetal period being plotted by monthly increments while the postnatal graph uses intervals of a year. Certain simple comparisons might perhaps make the growth rates involved take on more significance. During the second month, embryos tend to grow approximately a millimeter a day in sitting height. For the rest of gestation the daily increase averages about a millimeter and a half. Probably because a millimeter is so small compared with most of the dimensions with which we deal, this does not sound impressive. A more vivid realization of its import can be gathered by an extrapolation of this growth rate into postnatal life. A ten-

ture, the most useful illustration in the present connection would seem to be a group of outline diagrams, all drawn to natural size, to give a direct visual impression of the growth which occurs during the early part of development. Such a group is assembled in Fig 105. The embryos are shown in their chorionic vesicles because in these early stages such a considerable proportion of the product of conception is constituted by the extra-embryonic membranes. Since both patient and physician tend to think of embryonic age in relation to the interrupted menstrual cycle, the drawings have been arranged along a time line on which the menstrual history is indicated.

The marked flexion of the body and the bulging thoracic prominence caused by the heart make it impossible to get satisfactory frontal views of young embryos by photography. To draw the body as if it were straightened requires its graphic reconstruction from a series of different angles and inevitably involves the taking of some liberties with proportions. Nevertheless, when this is carefully done, one is repaid with interesting views (Fig 106) which not only make it possible to see what is going on in the facial region but also bring out certain of the characteristic proportions of the embryonic body from a point of view which makes them easier to compare with familiar adult conditions. The relatively enormous head, the conical shape of the thorax due to the unexpanded condition of the lungs, the protuberance of the upper abdomen because of the great size of the liver, and the startling slenderness of the slowly developing hips and legs are apparent at a glance. So also is the tail, which is so well developed for a time before its regression and concealment by the growing buttocks.

Formation of the Face Certain general considerations with reference to the development of the cephalic region were introduced in Chapter 5. We noted the fact that the neurocranial portion of the head was precocious and that the visceral portion arising from the gill arches differentiated somewhat later. We established also the general manner in which the visceral arch complex would be involved in the formation of the circumoral part of the face. It will be recalled that cephalic to the stomodaeal depression the upper jaw is formed by the fusion of the maxillary processes with the nasomedial processes, and that the mandible is formed, caudal to the stomodaeum, by the coalescence mid-ventrally of the right and left halves of the mandibular arch. In Chapter 14, the processes involved in the formation of the jaws and the teeth are to be taken up in some detail. It is sufficient here, therefore, to fix in our mind the second intra-uterine month as the period in which the main facial structures are established in essentially their definitive relationships.

It is true that the face of a human embryo at the end of the second month is quite simian in the breadth and flatness of the nose, and in the receding character of the chin. There is, nevertheless, no part of the adult face that is not, even thus early, present in recognizable form and in nearly its adult positional relationships (Figs 106, 247, 248). Perhaps the lowness of the external ears, reminiscent of their origin from the tissue about the hyomandibular

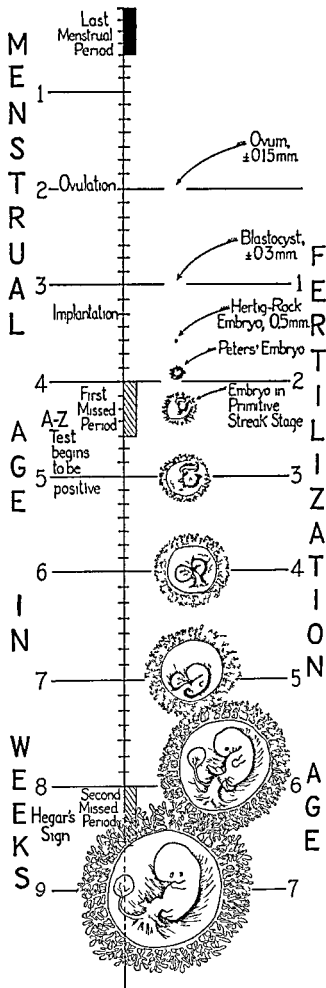


FIG 105 Diagrams showing actual size of embryos and their membranes in relation to a time scale based on the mother's menstrual history

cleft, is the most strikingly primitive thing about the head at this stage of development

The eyes, arising as they do from primordial outgrowths of the forebrain, first appear on the surface of the head merely as vague, rounded elevations (Fig 52) During the sixth week, the growing optic vesicle clearly outlines itself beneath the thin overlying ectoderm (Fig 59) By the end of the seventh week (Fig 62), the beginning of the formation of the eyelids strongly emphasizes the eye as a facial feature Eyebrows and eyelashes begin to be visibly developed during the latter part of the fifth or early in the sixth month

During more than half of intra-uterine life the eyes develop behind sealed eyelids, the lids meeting and fusing in the ninth week and not reopening again till the seventh month This means that unless its birth is hopelessly premature a human infant is born with its eyes open and does not have the period of closed lids prolonged for a time after birth as is the case with kittens and puppies

External Genitals It is not possible to tell the sex of an embryo by examination of the external genitals until the end of the second, or the beginning of the third month of development The primordia of the external sexual organs make their appearance well prior to this time but they are said to be "indifferent" because they exhibit only certain noncommittal tissue masses which later will be molded in one direction or another as the sex of the embryo becomes evident There is a conical local elevation in the mid-ventral line a little cephalic to the cloaca, which is known as the genital tubercle (Fig 106) This tubercle becomes the penis if the embryo is a male, or the clitoris if it is a female On the caudal aspect of the genital tubercle are slender folds (the genital or urethral folds) flanking a median (urethral) groove If the embryo is a male, these two folds close the urethral groove to form the penile urethra, in a female, they remain separate and form the labia minora (Figs 381, 382) Heavier, more laterally located folds become the scrotal pouches of the male or the labia majora of the female In the male, it is usually late in the seventh or early in the eighth month when the testes descend into the scrotum

Appendages The appendage buds make their appearance at about the transition from the fourth to the fifth week of development (Fig 58) During the sixth week, the terminal portion of the bud, which is destined to form the hand or the foot, becomes somewhat expanded and flattened with a curious marginal flange at its free border (Fig 60) Four radial grooves in the marginal flange early suggest the formation of the digits (Figs 61, 62, 107) The five thicker areas between the grooves grow rapidly and soon project beyond the main mass to form the fingers and toes As early as the eighth week, the growing thumb begins to diverge widely from the rest of the fingers (Fig 107, C) Similarly, the young great toe starts to develop at a truly ape-like angle to the rest of the foot (Fig 108, E)

During their development, the limbs undergo important changes in their axial position Let us consider the anterior appendages first because it is easy to mimic the positional changes with our own arms The young arm-buds

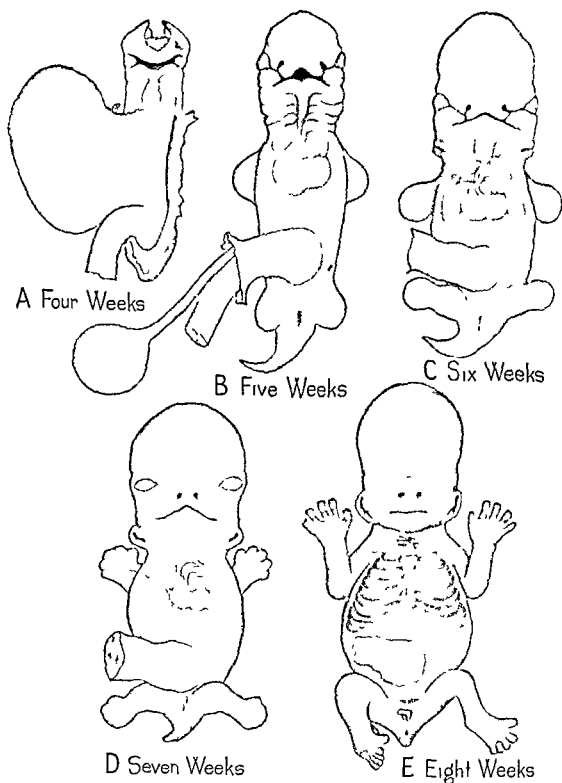


FIG 106 Frontal views of a series of young human embryos, drawn as they would appear if the body curvature had been straightened (After William Patten)

both lying astonishingly close to the chin (Fig 109, F) With the postnatal assumption of erect posture, the tibial-great-toe side of the leg is rotated mesiad This is of course the side of the leg which is homologous with the radial-thumb side of the arm and which was originally the cephalic border of the young appendage bud Consequently, one would expect to find the great-toe side of the foot supplied by nerves arising more cephalically than those supplying the outer side of the foot (Fig 183)

Integumentary Structures The epithelial layer of the skin in the early part of fetal life is exceedingly thin, so that the color of the underlying dermal

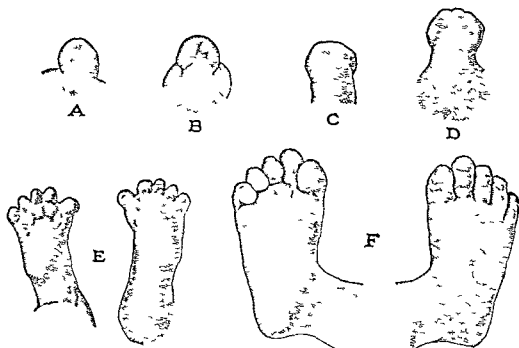


FIG 108 Stages in early development of the lower extremity (After Retzius, from Scammon, in Morris "Human Anatomy") A, Posterior limb bud of an embryo 12 mm long B, Posterior limb bud of an embryo 15 mm long C, Posterior limb bud of an embryo 17 mm long D, Foot and calf of an embryo 19 mm long E, Two views of the foot and ankle of an embryo 25 mm long F, Two views of the foot of a fetus 52 mm long

layer of vascular connective tissue shows through Moreover, it is not until relatively late in fetal life that there is any fat stored in the subcutaneous layers Consequently, a fetus prematurely born in the sixth or early part of the seventh month looks red and wizened to a degree which gives it, paradoxically, the appearance of weather-beaten old age Beginning late in the seventh month, fat is stored in the subcutaneous layers and the body normally exhibits a rapidly increasing plumpness as full term is approached This tendency to lay on cushioning masses of subcutaneous fat, coupled with the prominence of the abdomen because of the great size of the liver, gives a healthy newborn infant the type of figure made so familiar by Raphael's cherubs

Indications of the development of hair follicles can be seen in histological sections of the integument as early as the end of the third month Hair does

project outward almost at right angles to the lateral surface of the body (Fig 106) [Stand erect and hold the arms out horizontally, thumbs up, palms forward] With the formation of the elbow joint, the forearm and hand bend ventro-mesially [Without dropping the upper arm at the shoulder, or rotating the elbow joint, flex your elbows bringing the palms of your hands against your chest] Next, the arm drops into positions which seem more natural to an adult [Drop your elbows to your sides, letting the wrists cross each other loosely under the chin] This is the characteristic arm position for the rest of intra-uterine life. The final position, characteristic of man in his erect posture,

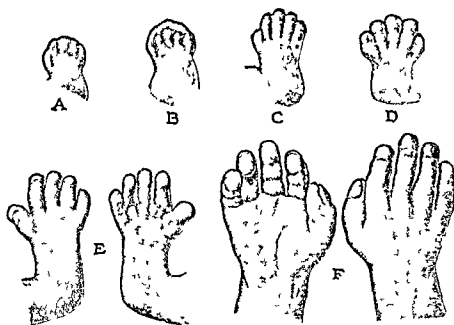


FIG 107 Stages in early development of upper extremity (After Retzius, from Scammon, in Morris "Human Anatomy.") A, Anterior limb bud of an embryo 12 mm long B, anterior limb bud of an embryo 15 mm long C, Anterior limb bud of an embryo 17 mm long D, Hand and forearm of an embryo 20 mm long E, Two views of the hand and forearm of an embryo 25 mm long F, Two views of the hand of a fetus 52 mm long

is attained by letting the arms hang freely from the shoulders. This involves a varying amount of rotation according to the position of the palms. If the palms are held forward and the thumbs outward, the outer part of the arm will be what was primitively the cephalic margin of the young appendage bud. This is nicely recorded by the distribution of the segmental nerves to the adult arm, the outer part being supplied by the more cephalic nerves and the inner part by those which arise farther caudally (Fig 183)

The primary position of the legs is similar to that described for the arms. When the knee joint is formed, however, the flexion is in the reverse direction to that exhibited by the elbow. The young human fetus, therefore, carries his appendages in a characteristically quadruped position [Look at Fig 92 or Fig 109, E, with the body held horizontally] As the appendages grow in length, they become more and more sharply flexed, with elbows and knees



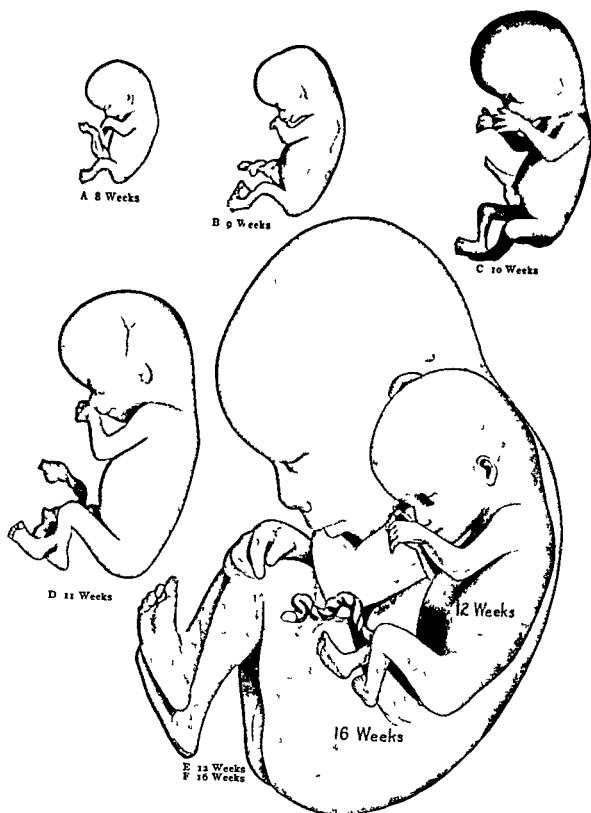


FIG 109 Human embryos between 8 and 16 weeks, actual size A-D, From photographs of embryos in the University of Michigan Collection E, F, Re drawn, with slight modification, from DeLee "Obstetrics"

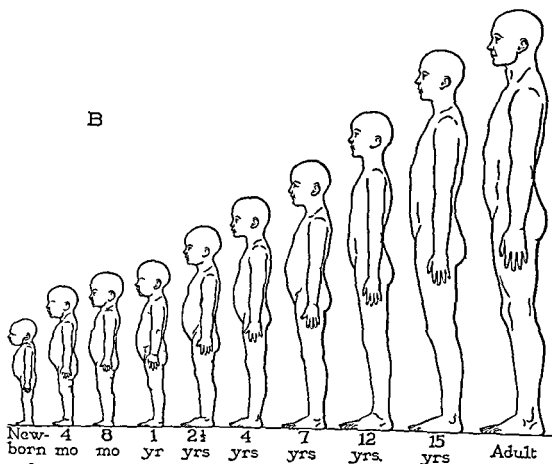
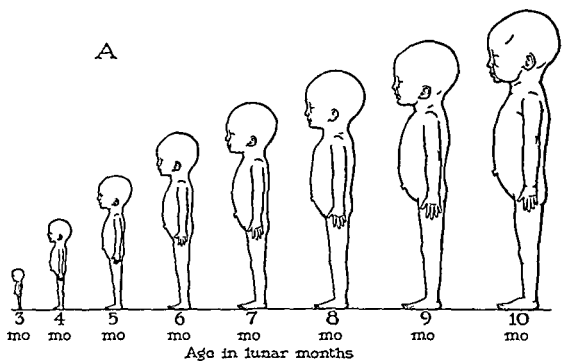


FIG 112 Series showing growth and development of the form of the body, left lateral views A, Eight fetal stages, based on the empirical formula of Calkins and Scammon, Proc Soc Exp Biol and Med, Vol 22, 1925 B, Ten postnatal stages, based on Schadow (From Morris "Human Anatomy")

not, however, become grossly recognizable on the body surface until the fifth or sixth month. The hair follicles of the face and scalp and such specialized areas as the eyebrows and eyelashes are a little ahead of the body hair in their development. The first body hairs of the fetus are very fine and closely spaced so that they constitute a downy coat known as the *lanugo*. It is usually during the seventh month that the *lanugo* is best developed. Thereafter it begins to be shed and replaced by coarser hairs, much more sparsely scattered.

Later Changes in Body Proportions Some time toward the end of the second or beginning of the third month of development, "when it begins to look human," it is usual to drop the term embryo and to speak of the product

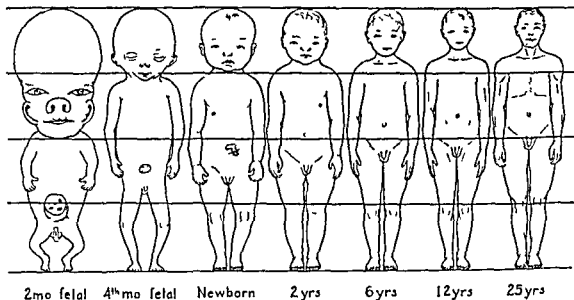


FIG. 111 Two fetal and five postnatal stages drawn to the same total height to show the characteristic age changes in the proportions of various parts of the body (Redrawn from Scammon)

of conception as a fetus. There seems no very good reason to worry about the precise time when this change in designation should be made or to insist on the rigid following of this usage which is kept more as a matter of tradition than because it serves any useful purpose. In the so-called fetal period of pregnancy, the most striking external changes are in the growth of parts already laid down during the first two months. A pictorial summary of the size increases from the eighth through the twenty-fourth week of pregnancy is given in Figs. 109 and 110. Beyond this age, actual size representations will not go on the available page space of a book such as this, and reference must be made to the graphs of Fig. 103 for normal dimensions.

The change in the relative size of different parts of the body is fully as interesting as the rate of increase in the body as a whole. An exceedingly valuable method of emphasizing differences in bodily proportions is to reconstruct the younger stages to the same total height as the definitive stage toward which they are growing. This painstaking method which has been very

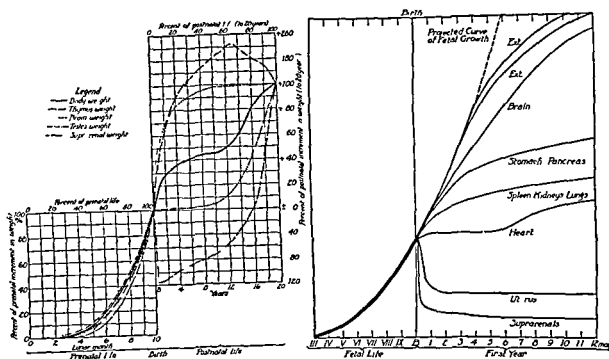


FIG. 113. Graphs showing common type of growth curve followed by a diverse group of organs before birth, and the transition to a variety of types of growth curves after birth (After Edith Boyd, "Outline of Physical Growth and Development")

ORGAN WEIGHT IN RELATION TO BODY WEIGHT AND LENGTH AT BIRTH

Body Weight (Gm)	750- 1,250	1,250- 1,750	1,750- 2,250	2,250- 2,750	2,750- 3,250	3,250- 3,750	3,750- 4,250
No. Cases	193	172	121	94	168	125	70
Organ	Arithmetic Mean Organ Weights in Grams						
Thyroid	1.1	1.3	1.4	1.8	1.8	2.4	2.4
Thymus	3.1	5.1	8.5	9.3	9.9	10.8	15.3
Heart	7.6	10.8	14.5	17.9	20.1	21.7	25.4
Lungs	25.2	33.7	44.2	49.5	54.7	59.4	64.0
Liver	49.2	66.3	87.9	105.8	140.4	151.5	185.1
Spleen	2.1	4.0	5.8	7.6	9.7	11.1	12.2
Pancreas	1.2	1.6	2.1	2.8	3.4	3.6	3.9
Kidneys	9.7	13.6	18.3	21.1	23.6	26.6	29.3
Adrenals	3.3	4.3	5.3	6.9	7.6	9.3	10.5
Brain	160.6	226.8	289.2	332.6	390.9	429.6	402.9
Mean body weight	999.0	1,477.0	2,006.0	2,508.0	3,005.0	3,439.0	3,945.0
Crown heel Crown rump	Body Length in Centimeters						
	36.5	41.5	45.7	48.4	50.9	52.6	54.0
	24.7	27.9	30.9	32.9	34.8	36.3	37.3

effectively used by Scammon and his co-workers in portraying the results of their quantitative studies of growth is exemplified in Fig 111. Such a figure shows relative proportions more vividly than volumes of description. One can not miss such things as the tremendous relative size of the embryo's head, the setting of the head almost directly on the shoulders with practically no neck, and the exceedingly small hips and posterior appendages. At the same time, this graphic method shows equally clearly the series of changes by which adult proportions are reached. The changes in bodily proportions are graphically shown in Fig 112 by a different method which emphasizes especially well the rate of increase in the total size of the body.

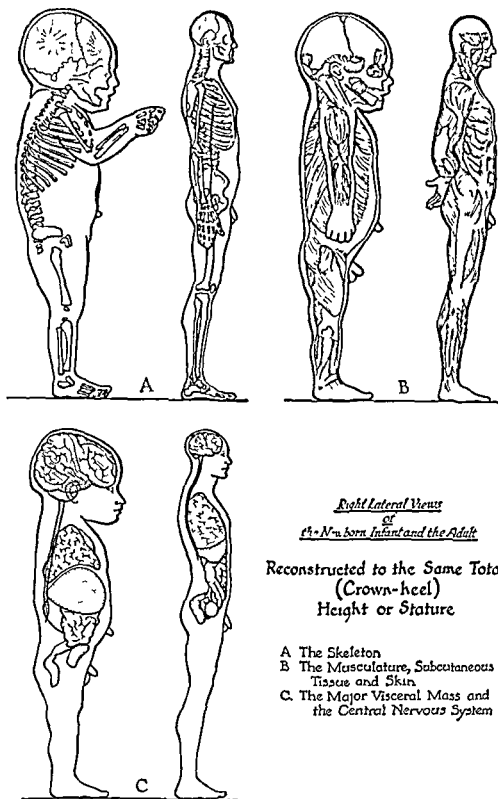
GROWTH OF ORGAN SYSTEMS

The discussion so far has centered about the growth of the body as a whole and some of the striking changes in its external appearance, and in its proportions. It must be realized that growth does not take place synchronously or at equal rates in all regions of the body, but that each organ and part has its own characteristic life history. In certain vestigial organs such as the mesonephros, the cycle is greatly abbreviated. Other organs, as for example the thymus, persist during childhood and then undergo involution, the organs of the central nervous system develop relatively early, while the reproductive organs have their period of rapid growth much later. These matters will come up in subsequent chapters dealing with the development of each of the organ systems, and it would carry us afield to go into them in any detail here. It seems pertinent, nevertheless, while we are discussing the matter of growth, to include Fig 113 at this point to suggest some of the more striking differences in the postnatal growth rates of different types of organs. It is particularly interesting to note the fairly uniform rate of growth maintained by such a group of organs while they are under the relatively sheltered and stable conditions of intra-uterine existence, in contrast with the wide divergence they exhibit after birth.

Some of the more striking changes in the relative proportions undergone by the different organ systems between birth and maturity can be shown pictorially. The recent work of Wilmer has made available silhouettes of the newborn and adult bodies reconstructed to the same height with the organ systems drawn in to proper scale. In Fig 114, A is indicated the skeletal system, which in spite of striking differences shown in the proportions of certain of its parts, constitutes about 15 to 20 per cent of the total body weight in both the newborn and the adult. Fig 114, B shows the muscular system which in the newborn constitutes some 25 per cent of the body, whereas in the adult it is 40 to 45 per cent. In the C pair of figures is depicted the central nervous system, constituting about 15 per cent of the newborn body while it is a mere 2.0 to 2.5 per cent in the adult. The same figures show also the major visceral masses amounting to about 9 per cent of the body at term, while in the adult they are in the neighborhood of 5 to 7 per cent. These examples are enough to indicate that we can not think loosely of a newborn infant as being already an

adult in miniature. In a 20-odd year period of growth, birth is merely an incident which dramatically confronts us with a body swiftly prefabricated in concealment and with all its major parts assembled but still, in detail, far from its finished form.

While we can not go farther into the growth rate of the different organs of the body, the size that they may normally be expected to attain by the time of birth is information that is of value in connection with autopsies on newborn infants. Since many of the deaths which occur at or near the time of birth are due to abnormalities of development which directly or indirectly involve changes in the growth rate of the organs, it seems pertinent to include here for reference an abridgment of the Potter-Adair table of normal organ weight in relation to body weight at the time of birth. (See table on p. 201 from Potter and Adair, 1940, Table 16, p. 33.) Abnormalities of growth can be discussed more conveniently in the following chapter in relation to other malformations.



*Right Lateral Views
of
the Newborn Infant and the Adult*

Reconstructed to the Same Total
(Crown-heel)
Height or Stature

- A The Skeleton
- B The Musculature, Subcutaneous Tissue and Skin
- C The Major Visceral Mass and the Central Nervous System

FIG 114 Right lateral views of the newborn and adult reconstructed to same height or stature (From Scammon, after Wilmer, in Morris "Human Anatomy")

vidual, successful artificial production of complete twins seems possible. While these experiments clearly indicate the sort of separating process which must occur, the heavy membrane (thickened zona pellucida) which surrounds the mammalian ovum during its early divisions (Fig. 33) would seem to be a definite bar to any fortuitous separation of the blastomeres during the cleavage stages. It becomes necessary, therefore, to look for a similar process of separation which might occur at a somewhat later stage of development.

A very suggestive condition occurs in the development of the armadillo, where identical quadruplets are regularly produced by the subdivision of the inner cell mass of a single blastocyst into four parts, each of which develops into a complete embryo. Specimens of sheep and pig embryos recovered at critical ages offer evidence that fortuitous separation of the inner cell mass (Fig. 115, A) sometimes occurs in forms which have an early blastocyst similar to that of primates. Another closely comparable condition is not infrequently encountered in large-yolked forms in which the homologue of the inner cell mass is a flattened disk of cells on the surface of the yolk-sphere. Instead of a single body axis developing in this mass of proliferating cells, we may find two (Fig. 123). In either mammalian or sauropsidan embryos, provided such twin centers of organization appear far enough apart so they do not interfere with each other's growth, each center seems to have the potentiality of organizing a complete body (Fig. 115, A-C). From such collateral evidence, the implication seems clear that identical twins in man arise from a single fertilized ovum as the result of its subdivision into two independently growing centers, either at the inner cell mass stage or the immediately succeeding primitive embryonic disk stage.

As to the possible causative factors behind such a process, the situation is by no means so clear. There is abundant experimental evidence indicating that environmental disturbances such as marked changes in temperature, or alterations in the chemistry of the surrounding medium or in oxygen supply, have a disturbing effect on centers of growth and differentiation. Reasoning from these facts, an ingenious hypothetical interpretation has been advanced to the effect that when the normally dominant growth center is so disturbed, two or more adjacent areas with latent similar potentialities may take over a rôle they would not have assumed had they remained under the dominance of the primary center. This interpretation is consonant with the facts known at present, but we must frankly admit that our knowledge is as yet too fragmentary to justify more than a tentative suggestion that the explanation may well lie along some such lines.

Frequency of Multiple Births The discussion up to this point has been phrased in terms specifically applicable to twins and twinning. The same principles can be broadened to apply to multiple births in general. Quadruplets, for example, might be all fraternal, having arisen from four separate ova, or they might be monovular, all having arisen by division—and then immediate redivision—of the inner cell mass in the manner which occurs in twinning. They might, also, be of mixed origin, two being fraternal twins and

Twins; Double Monsters and Teratology

TWINS

Types of Twins It is a matter of common knowledge that some twins look so much alike that it is difficult to tell one from the other, whereas other twins may resemble each other but little and may even be of opposite sexes. It is less generally known that there is a biologically important difference in the manner of origin of similar and dissimilar twins. The production of two infants by coincident gestation is most commonly the result of the liberation and fertilization of two separate ova. In such cases, the infants are spoken of as fraternal twins (diovular twins). They may or may not be of the same sex and may or may not resemble each other strikingly. Really, they are "litter-mates" in the same sense that this expression is applied to the offspring of lower mammals in which plural births are the rule.

In contrast to this situation, "similar," "identical," or "duplicate" twins, as they are variously termed, are derived from a single fertilized ovum which has at a very early stage of development become divided into two independently growing cell masses each of which eventually forms a complete individual. For this reason, twins of this type may be designated as monovular. The fact that two such individuals have exactly the same chromosomal heritage explains their extraordinary physical and mental likenesses and also the fact that they are always of the same sex. Monovular twins are intensely interesting from psychological and sociological angles as well as from the biological, for they offer an unequalled opportunity for studying the effects of different methods of training and different environmental factors on a pair of individuals with the same genetic constitution.

Monovular Twinning We have no complete series of developmental stages showing us the precise mechanism of monovular twinning in the higher mammals. Circumstantial and collateral evidence is, however, abundant and sufficiently clear in its implications so that there seems little doubt as to the general sequence of events. We know that in many of the lower animals twinning can be brought about experimentally merely by separating the blastomeres during the early stages of cleavage. How far along in the process of cleavage this separation may be carried out varies greatly among different species, and seems to depend on how early the differential sorting out of developmental potentialities begins. As long as the separated cell groups each contain all the potentialities necessary for the formation of a complete indi-

two being monovular. Triplets might be fraternal or a combination of a pair of monovular individuals with another sibling arising from a second ovum which did not undergo division. The frequency with which multiple births occur varies somewhat in different races. The figures for the United States

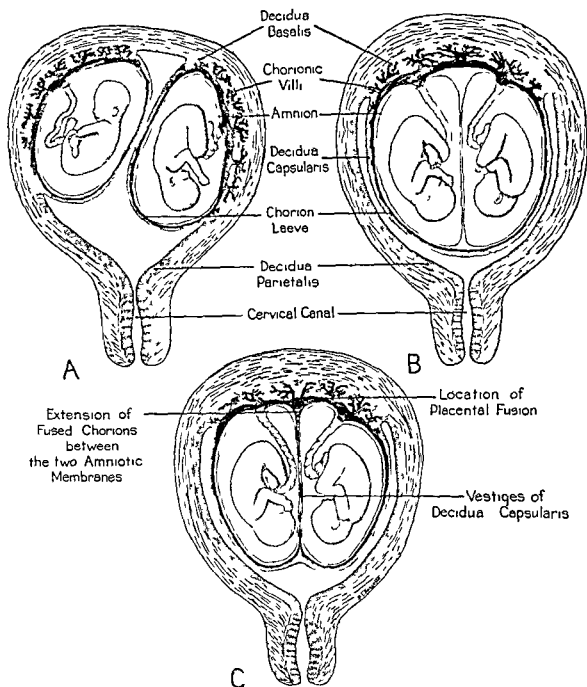


FIG. 116 Schematic diagrams showing three different relations of the fetal membranes of twins (Modified from Bumm's figures in Kollmann's "Atlas") A, Diovtular twins with entirely independent membranes B, Monovular twins C, Diovtular twins implanted close to each other with resultant secondary fusions of their membranes

indicate that twins may be expected once in every 88 births, triplets once in 88 squared, and quadruplets once in 88 cubed. Instances of more than four births at a time occur too infrequently to justify an attempt to put them on a statistical basis. The maximum number of simultaneous births well authen-

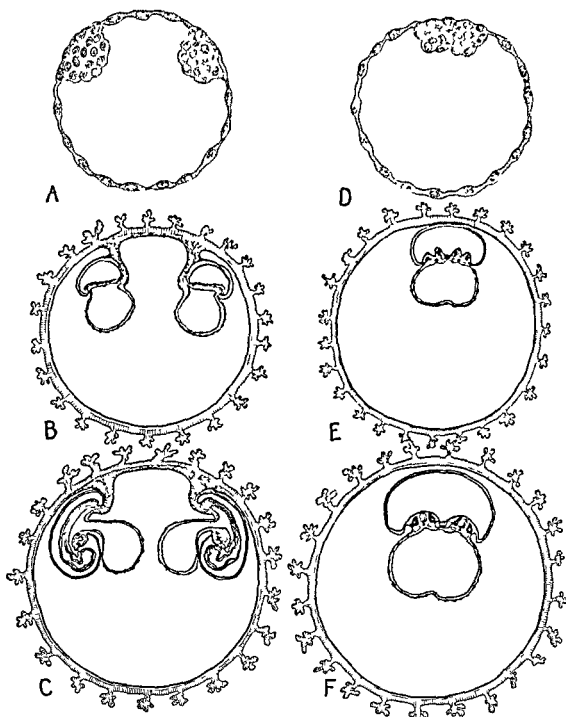


FIG 115 Schematic diagrams indicating the manner in which single-ovum twins are believed to be related within the blastodermic vesicle (Based, in part, on the work of Corner and Streeter) A-C, The inner cell mass is depicted as separating into two parts, early and completely. Such conditions might be expected to lead to the formation of entirely independent and physically normal twins. D-F, The inner cell mass is represented as carrying out a somewhat delayed and incomplete separation. Such conditions might be expected to lead to the formation of conjoined twins.

examination of the membranes separating the two fetuses for vestiges of decidua capsularis is all too frequently neglected

Sometimes the relations of the extra-embryonic membranes give us an interesting sidelight on the manner in which the division might have occurred in the formation of the twins. This is particularly likely to be the case in those rare instances when very young twin embryos are recovered. An especially interesting case of human twins of about six weeks' fertilization age in which the embryos were attached to a common yolk-sac has been described by Arey (Fig 117, A). Fig 117, B and C, indicate plausible hypothetical steps toward the condition found.

DOUBLE MONSTERS

A rare accident in the development of monovular twins is to have them go through pregnancy joined together and be born at full term as a "double monster." The degree of fusion varies from a slender connection of superficial tissues joining two almost completely independent individuals, to fusions involving the skeleton and viscera throughout most of the trunk so that only the head, or only the posterior part of the body, appears as double. The place and the angle of fusion also differ so that over the years medical museums have assembled a great variety of these weird freaks. Any classification of them is of course arbitrary, but it has proved convenient to separate such double monsters for discussion into two main categories: (1) Equal conjoined twins, in which the two fused individuals are fairly symmetrically developed, and (2) unequal conjoined twins, in which one individual is decidedly smaller than the other. The smaller member of such an unequal pair is likely to be markedly ill-formed and its appearance may suggest that of a grotesque parasite on the larger, more normal twin.

Equal Conjoined Twins Symmetrical double monsters may be grouped for study, and named, according to the part of the body in which the fusion exists. Three simple and convenient groups used by Schwalbe are upper, middle, and lower unions. Upper unions include those affecting primarily the head-neck level, middle unions those between the neck and the umbilicus, and posterior unions those primarily caudal to the umbilicus. Fusions at any of these levels may be back to back, face to face, or side to side. If this general idea of the possibilities of unions at three levels, from three angles, and to varying degrees, is borne in mind, the major types of double monsters which may be encountered can be figured out without unduly taxing the memory. The matter is further simplified by the practice of naming them, as far as possible, with the suffix *-pagus* (Greek root = fastened) tacked onto a familiar anatomical term designating the region of fusion, as for example, *craniopagus*, head-to-head union, *thoracopagus*, chest-to-chest union, *pygopagus*, rump-to-rump union, and so on (Fig 118).

For some reason, side-to-side fusions seem to start either at the head or the rump end and never at thoracic levels. There is, however, a tendency for lateral fusions to be quite extensive, and the thorax is frequently secondarily

ticated for man appears to be six,¹ and the maximum with survival of all the offspring, five. These figures are for multiple births without regard to whether the offspring are monovular, fraternal, or a combination of the two.

With regard to twins, there is fairly good evidence indicating that approximately three-fourths of all cases are fraternal and only about one-fourth monovular. With regard to multiple births involving more than two individuals, in the absence of adequate data we can only assume that a similar preponderance of fraternal types exists. The tendency to produce twin offspring which appears in certain families seems to be due to a hereditary tendency to mature more than the single ovum usually produced by women at a given ovulatory period. No evidence at present available indicates anything other than an entirely fortuitous occurrence of monovular twinning.

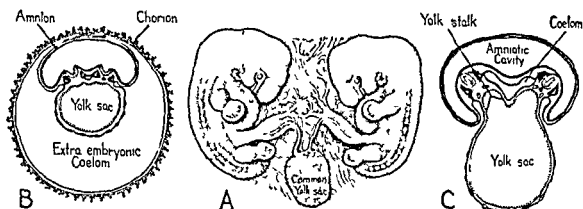


FIG. 117. Monovular twins with a common yolk-sac. A, Drawing from an actual case involving 12-mm human embryos (After Arey). B, C, Hypothetical diagrams indicating how the conditions shown in A might have been established.

Extra-embryonic Membranes in Twins. There is a rather widespread belief that it is possible to tell whether twins are fraternal or monovular by inspection of the after-birth. Although this is often true, there must be some reservations about conclusions so reached. If the membranes of each fetus are complete and entirely separate (Fig. 116, A), there can of course be no doubt as to the origin of the twins from separate ova. Where there is clearly a single chorionic vesicle containing both fetuses (Fig. 116, B), the presumption is that the twins are monovular. The difficulties come in connection with fraternal twins implanted very close together within the uterus. When this occurs, secondary fusions of originally separate placentas may reach a degree of intimacy that is easily confused with conditions in monovular twins (cf Fig. 116, B, C). When one remembers the torn condition of the membranes as they are presented for examination after delivery, and the fact that the decidua capsularis is usually so reduced that it can not be identified by the unaided eye, the difficulty of making a correct decision by mere inspection of the placenta is obvious. The necessary additional step of making a histological

¹ Barfurth (1895) mentions a stone tablet in Germany marking the site of a house where seven infants were said to have been born simultaneously. There is too little information available, however, to regard this as a substantiated case of multiple births.

involved. This tendency to spread over more than one region means that the lateral fusions do not readily lend themselves to designation with the -pagus suffix so useful with the more localized unions. It is customary to name them on the basis of the part which remains double—*duplicitas anterior* or *duplicitas posterior* (Figs 119, 120)

Fortunately, most of the more intimately joined double monsters, such as

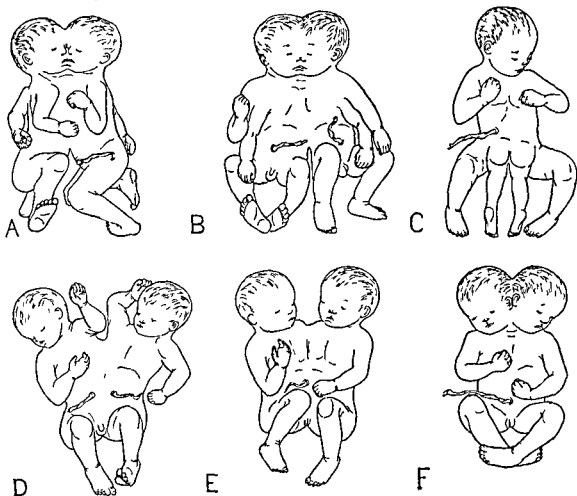


FIG 119 Sketches of conjoined twins in which the fusion is more extensive than in the cases illustrated in the preceding figure. A, B, Fusions involving both thorax and head (cephalothoracopagus). C, Upper parts of bodies completely merged but lower parts still separate (*duplicitas posterior*). D, Complete fusion of lower parts of bodies but upper parts separate (*duplicitas anterior*). E, F, Conjoined twins in which the extent of the anterior duplication has been reduced by fusion of the thorax (E) and by fusion of the thorax and partial fusion of the head (F).

the cephalothoracopagus illustrated in Fig 120, fail to survive. Occasionally, less extensively joined twins live, usually to find their way into the circus side-shows.² A very common—and pertinent—question asked in connection with these individuals is why no attempt is made to separate them surgically. Such a procedure is theoretically possible if the union is superficial, but there is all too likely to be the sort of interlocking relation between the internal organs

² The lay expression "Siamese twins" generally used to mean any type of conjoined twins came from such publicizing of a xiphopagus pair brought to this country from Siam.

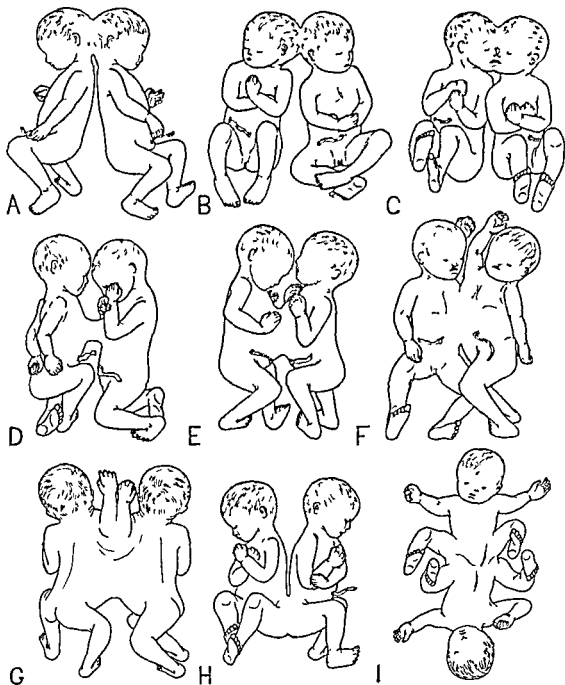


FIG 118 Diagrams illustrating various types of conjoined twins (Adapted from a number of sources) In all the cases here sketched both heads and both pairs of appendages retain their identity Contrast this group with the cases shown in Fig 119 in which more extensive fusion has taken place A-C, Head to-head fusion (cephalopagus) The three cases show different angles of fusion D-G, Different degrees and angles of chest to chest fusion (thoracopagus) H, I, Two cases of rump-to rump fusion (pygopagus)

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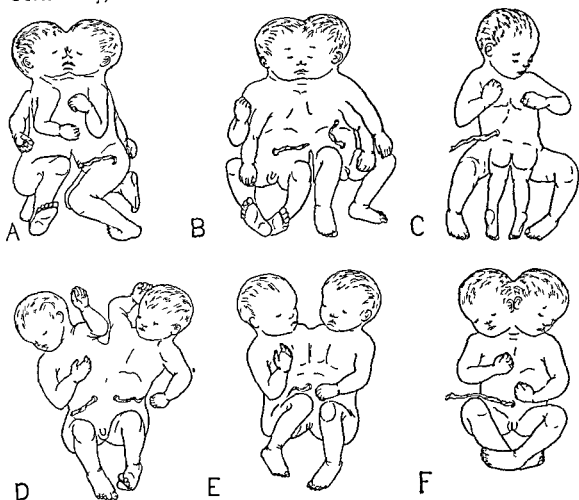


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² The lay expression 'Siamese twins' generally used to mean any type of conjoined twins came from such publicizing of a xiphopagus pair brought to this country from Siam.

shown in Fig 121. Thus, of course, means that any surgical procedures for the separation of conjoined twins can be undertaken only after careful preliminary studies including adequate roentgenologic examination.

Unequal Conjoined Twins The origin and the possible sites of union of unequal conjoined twins are the same as for the corresponding symmetrical

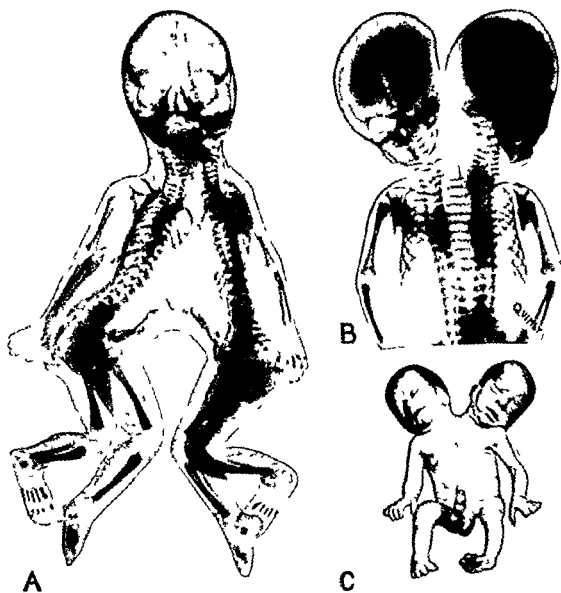


FIG 120 Nature of the skeletal fusions in conjoined twins A, X-ray of cephalothoracopagus (From Dondero, *Malformazioni Fetalì*, 1937) B, X-ray of duplicitas anterior (After Quimby, *Am J Roent*, Vol 2, 1914-15) C, Photograph of case of duplicitas anterior (After Quimby, *loc cit*)

double monsters. The only essential difference is that in the case of the unequal pairs something happens which interferes with the development of one of the twins so that its growth lags, or normal differentiation fails to occur, or both processes are disturbed. When this difference is considerable, the smaller and less complete twin is commonly spoken of as "parasitic" on the larger and more nearly normal member of the pair. Examples of malformations of this type are shown in Fig 122.

Theories as to Formation of Double Monsters We are probably nearer to some understanding of the factors involved in the formation of double monsters than is the case with most developmental malformations. It is obvious that we must be dealing with a monovular twinning process which has gone awry. As we have seen, the collateral evidence from nonprimate material indicates that this type of twinning in man must involve either a separation

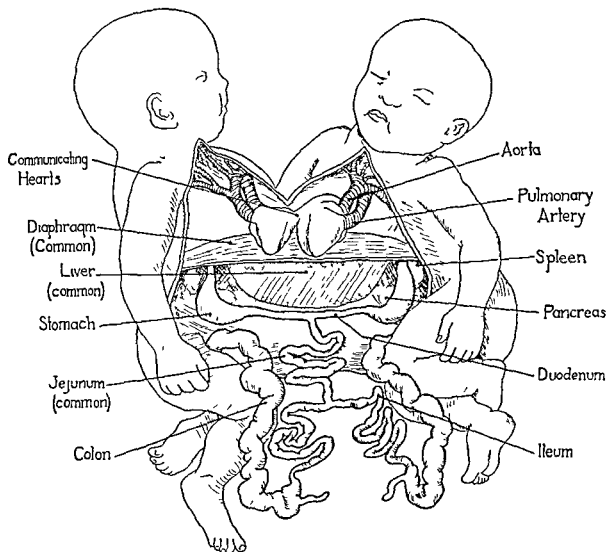


FIG 121 Semischematic diagram of a dissection of a thoracopagus to show the character of visceral fusion which may exist (Redrawn from Schwalbe *Missbildungen des Menschen und der Tiere*)

of the growing cluster of totipotent cells within the young blastocyst in the inner-cell-mass stage, or their regrouping at a slightly older stage around two centers of differentiation in the early embryonic disk.

Very closely akin to this second possibility—to all intents and purposes merely a temporal variant of it—is a third possibility suggested by Newman. He believes that there may be splitting of the axial area of differentiation *after* it is established in the embryonic disk. It is entirely possible that in different instances any of these methods may be operative. It is, moreover, by no means implausible that the time at which the separation occurs may be a critical

factor in determining whether normal twins or a double monster will result. Certainly early and complete separation of the inner cell mass (Fig 115, A-C) would seem to offer better possibilities for the formation of two complete and independent individuals, and the relatively late or incomplete splitting

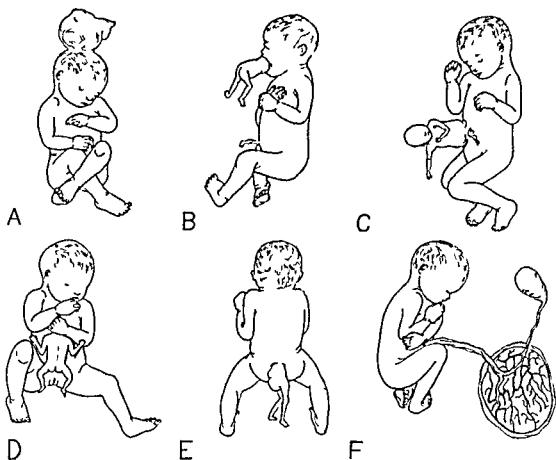


FIG 122 Unequal twins. In such cases the smaller member of a conjoined pair is often spoken of as a "parasitic twin," and the more nearly normal one as the "autosite."

A, Case in which body of reduced twin consists largely of a head. Because of the head to head fusion and the smallness and incompleteness of one member of the pair the technical designation of such a case would be *cephalopagus parasiticus*.

B, Reduced twin attached to jaws of autosite (*epignathus parasiticus*).

C, Parasitic twin attached to epigastric region of autosite.

D, Parasitic twin attached to thorax of autosite (*thoracopagus parasiticus*).

E, Parasitic twin attached to rump of autosite (*pygopagus parasiticus*).

F, The case here sketched is not one of conjoined twins. In this instance the only connection between the twins is an indirect one by way of the common placenta. One twin is represented only by a malformed head. Whatever circulation reached this acardiac twin must have been pumped to it by the heart of the normal twin by way of common vascular channels in the placenta.

of the inner cell mass (Fig 115, D, F) would seem more likely to result in the formation of conjoined twins. The double chick embryos illustrated in Fig 123 are of the type that appear to have arisen by relatively late separations, and were probably on the way toward becoming conjoined twins.

A point of interest in connection with such embryos in laboratory animals

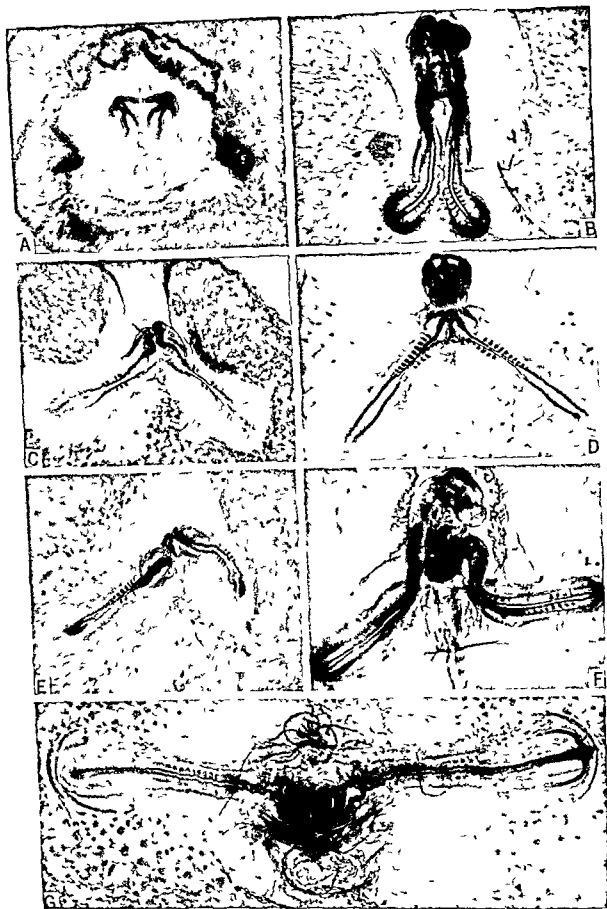


FIG 123 Double chick embryos showing some of the developmental steps involved in the formation of double monsters A, B, Two stages in formation of a thoracopagus (cf Fig 118, F) C, D, Two stages in formation of a cephalothoracopagus (cf Fig 119, A, B) E, F, Two embryonic stages that might lead to the formation of a thoracopagus parasiticus (cf Fig 122, D) G, Embryonic cephalopagus

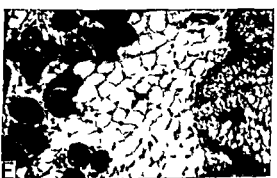
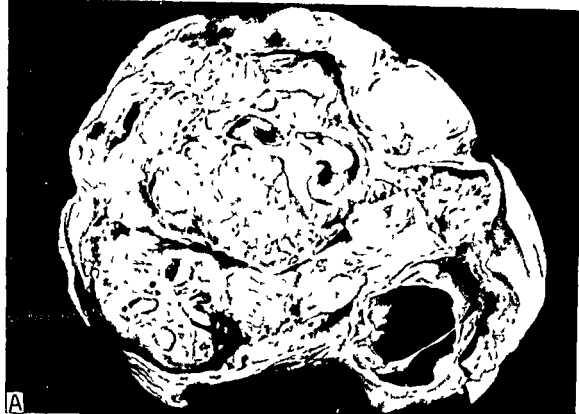


FIG 124 (For legend see p 217)

is the relative frequency with which they appear in the study of large groups of embryos obtained very early in development, as compared with the much smaller proportion appearing at the close of embryonic life. This difference indicates a very heavy mortality among such abnormal embryos during the developmental period. In all probability, a similar situation exists in man, and the very small number of conjoined twins born at full term represents an apparent incidence of the condition which has been greatly reduced by intra-uterine death and elimination.

Embryomata and Teratomata In the literature the term teratoma will be found applied to almost any kind of mixed tumor. Under this usage, the growths grouped together are exceedingly heterogeneous. As we learn more about them, it is appearing increasingly desirable to separate off one group of these mixed tumors under the name of embryomata. According to this usage, we would include under the embryomata those of the mixed tumors that had clearly differentiated organs or parts of organs representing all three of the primary germ layers. Put in another way, to be classed as an embryoma a tumor must exhibit enough of the fundamental parts characteristically present in a normal embryo to suggest that it arose from an aggregation of cells which under other conditions might have produced a complete individual. Such a usage implies acceptance of the interpretation that an embryoma starts as a potential identical twin which develops so poorly and with such defective molding of the body that its nature ceases to be evident except when its internal structure is investigated by critical dissection and microscopical identification of tissues and organs.

It is obvious that on such a basis there would be only an arbitrary distinction between a parasitic twin and an embryoma. Intermediate conditions are exhibited by cases of the type designated as included fetuses. Such a condition (fetus in fetu) is believed to arise when one member of a pair of conjoined twins, very early in development, starts to lag behind the other and eventually becomes encased in the body of the more normal twin. These included fetuses are usually greatly distorted as to bodily organization and grade into conditions one would prefer to designate as embryomata. About all that can be said by way of a basis of distinction is that one would call it an included twin as long as gross examination showed recognizable body topography that made its nature immediately apparent. When dissection and histological study of a formless mass is necessary to disclose its nature, one would call it an embryoma.

FIG 124 Teratoma of ovary (From a specimen acquired through the courtesy of Dr. Carl V. Weller.) A, Photograph, actual size, of gross specimen, cut open. B-G, Photomicrographs, $\times 135$, of small areas of histological sections from sample blocks of tissue taken at random from the gross specimen. The areas selected show: B, Choroid plexus, C, Hair follicle and sebaceous gland, mixed mucous and serous glands adjacent, D, An area of endochondral bone formation, E, Sweat glands embedded in adult and embryonic types of fat, F, Stratified columnar ciliated epithelium with mixed glands and cartilage adjacent, G, Patch of intestinal mucosa of type occurring in colon.

If the embryomata are split off as a separate group, the teratomata would then be defined as mixed tumors which showed tissues or fragmentary parts of organs derived from more than one germ layer but showing little or no suggestion of a normal architectural arrangement. One of the more commonly encountered teratomatous masses is the *dermoid cyst*. This growth contains such structures as skin, hair, sebaceous glands, nails, and teeth. Cartilage or bone may be present. It will be noted that the structures mentioned represent ectoderm and mesoderm but that there is no characteristic entodermal derivative. Dermoid cysts seem to have a strong tendency to arise in the gonads, especially the ovary. They are also likely to appear where ectodermal fusions occurred in the embryo, as, for example, the mid-dorsal line.

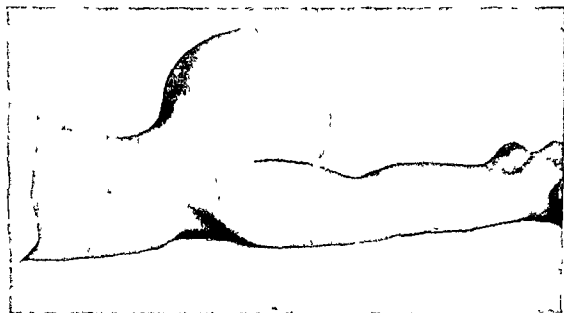


FIG. 125 Teratoma in sacral region—probably of primitive streak origin (Photograph, courtesy, Dr. Max Peet)

Other teratomatous masses appearing in the ovary or the testis may show disorganized fragments of organs with all three of the primary germ layers represented (Fig. 124). It is exceedingly difficult to postulate a logical series of developmental stages by which such growths could be interpreted as included twins, or embryomata, in the sense employed in this discussion. Although there may be some plausibility in the suggestion that an ovarian pregnancy could be the start of a teratoma of the ovary, the same line of reasoning will obviously not explain similar teratomata of the testes. It seems more logical to suspect that teratomata of the gonads may be neoplastic growths of the totipotent germinal tissue there present. In line with such a tentative interpretation are the large teratomata which are seen not infrequently in the sacral region (Fig. 125). They are most likely to appear where they could be accounted for on the basis of an unorganized growth of totipotent cells from the primitive streak region of the embryo. It must, however, be admitted frankly that considerable further study of these extraor-

dinary growths is necessary before any of the various interpretations of them can be supported with assurance

TERATOLOGY

Translating its roots literally, the word teratology means the study of monstrosities. The term is frequently more broadly used to include the study of any abnormality arising in the course of development. We have, therefore,

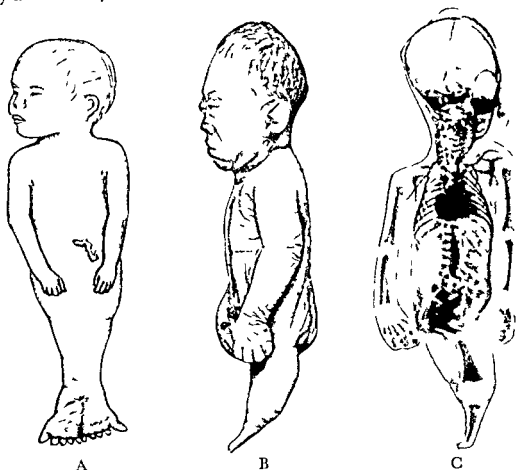


FIG 126 Cases of sirenomelus A, Sketch of a specimen (No. 1035) in the Koenigliches Pathologisches Museum of Berlin. Note that the two feet although fused can be separately distinguished,—hence the designation *Sirenomelus symphus dipus* B, *Sirenomelus apus* (After Dondero) C, X-ray of specimen shown in B (After Dondero) Note complete absence of the bones of the feet

already been in one of the fields of teratology in discussing conjoined twins and embryomata. Other fields would be malformations of the general external structure of the body due to factors other than distorted twinning and—using the term in its broadest sense—abnormalities of the internal organs. From the standpoint of convenience and clearness of presentation, it seems preferable to discuss the commoner abnormalities of each organ system in the chapter devoted to the development of the system in question. By so doing, each of the developmental aberrations will be thrown into the clearest possible contrast with the normal course of events from which it has diverged. Since we have already considered the formation of double monsters in connection

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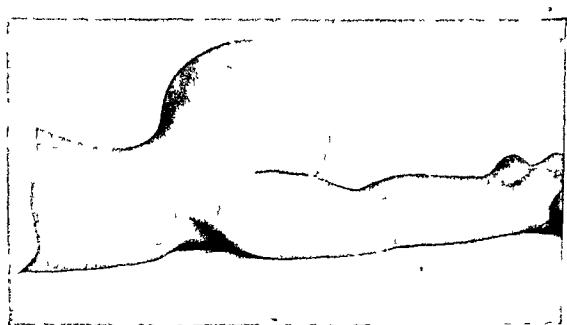


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(Photograph, courtesy, Dr. Max Peet)

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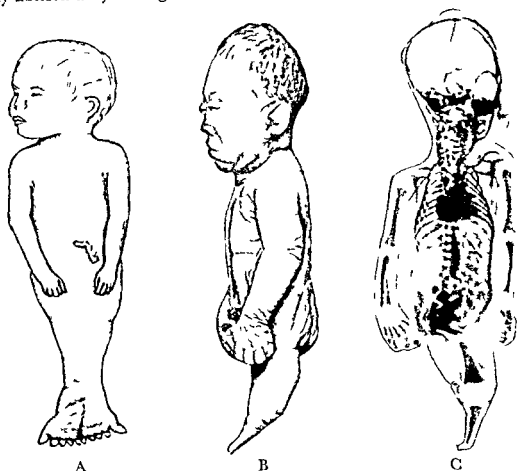


FIG 126 Cases of sirenomelus A, Sketch of a specimen (No. 1035) in the Koenigliches Pathologisches Museum of Berlin. Note that the two feet although fused can be separately distinguished,—hence the designation *Sirenomelus symphus duplex* B, *Sirenomelus apus* (After Dondero) C, X-ray of specimen shown in B (After Dondero) Note complete absence of the bones of the feet

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with twinning, and plan to defer the discussion of anomalies involving specific organs, there remain for consideration at this time malformations involving external body form, body proportions, or the molding of the appendages. Frankly, the conditions we are about to consider have little in common other than the fact they are developmental anomalies that can be considered here more conveniently than elsewhere. Let us first see what some of these anomalies are like, and then turn our attention to the possible causative factors.

Malformations Involving Legs and Arms Instead of growing independently, the two posterior appendage buds may fuse with each other to form a

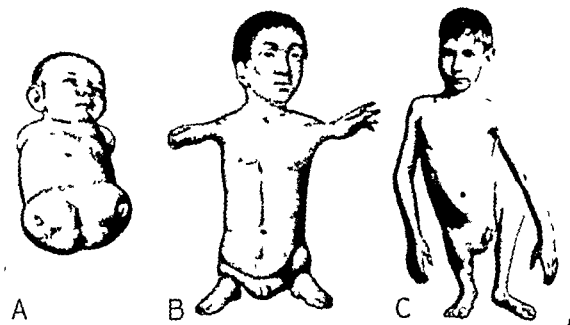


FIG 127 Developmental disturbances in formation of the appendages A, Amelia (After Broman) B, Phocomelia (From Broman, after Shatz) C, Distorted legs and hip joints (From Broman, after Royal College of Surgeons' museum specimen)

single tapering mass suggestive of a body which is fishlike in its caudal half (Fig 126). To the older anatomists who were well versed in classical mythology, this suggested the mermaid (siren) with the upper body of a beautiful woman and the tail of a fish, and so this condition received its name of *sirenomelus*. It would be interesting to know whether or not the original concept of the mermaid started from seeing malformed infants of this type and then developed by giving rein to the imagination in embellishing the condition.

Many other malformations occur which involve the legs, or both the legs and the arms. An exceedingly rare anomaly is complete failure of both pairs of appendages to develop, a condition known as *amelia* (Fig 127, A). There may be fairly normal-appearing hands and feet, which, by reason of failure of the limbs to elongate, seem attached directly to the trunk (Fig 127, B). This condition is known as *phocomelia* because of the resemblance of the malformed appendages to a seal's flippers. Less uncommon than the foregoing are developmental defects which are not so extreme. These may affect either

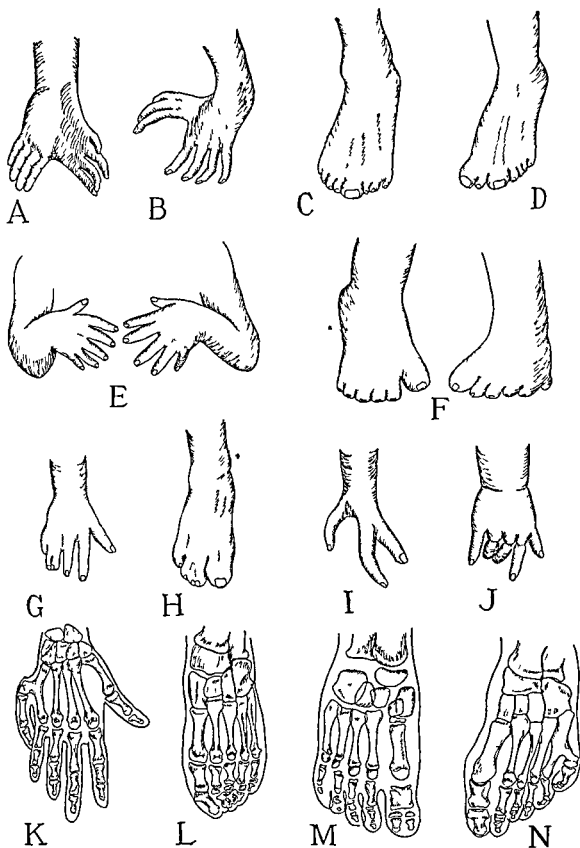


FIG 128 Various types of defects of hands and feet A, B, Double hand (dichurus) (After Corning) C, D, Double feet (diplopodia) (After Corning) E, F, Polydactyly (After Broman) G, Syndactyly of hand (After Broman) H, Syndactyly of foot (After Broman) I, Cleft, or "lobster-claw" hand (After Corning) J, Amputation of fingers (After Corning) K, Skeletal configuration in polydactyly of hand (After Broman) L, Skeletal configuration in syndactyly of foot (After Corning) M, Doubled great toe (After Corning) N, Skeletal configuration in polydactyly of foot (After Corning)

the arms or the legs alone or even a single arm or leg with all other appendages normal. An example of a case in which the two legs are asymmetrically deformed but both arms are normal is illustrated in Fig. 127, C.

Malformations of Hands and Feet In view of the complex processes of differentiation involved in the formation of structures such as the human extremities, it is not surprising that a variety of developmental defects should be encountered. Fortunately, none of them occurs with any frequency. A very uncommon but most striking anomaly appears to be due to a tendency for the entire extremity to divide distally, resulting in more or less complete duplication of the digits. When this involves the hand, the malformation is known as *dichurus* (Fig. 128, A, B), the corresponding anomaly of the foot is called *diplopodia* (Fig. 128, C, D). A similar process of duplication may involve only a single digit, resulting in the common type of *polydactyly* (Fig. 128, E, F). There may be a failure of the developing digits to become normally separated from each other, thus producing an anomaly known as *syndactyly* (Fig. 128, G, H). Still another disturbance is the failure of one or more digits to form, causing a condition known as *oligodactyly* (Fig. 128, I). Outline diagrams showing the nature of the distortions appearing in the bones in some of the foregoing types of anomalies will be found in Fig. 128, K-N. The strong tendency toward hereditary transmission of malformations of the extremities is vividly shown by the family groups depicted in Fig. 129.

There is another type of anomaly involving either the fingers or the toes which was interpreted by all the older writers as the result of *amniotic adhesions*. Bands of amniotic tissue were believed to constrict a digit, or even an entire limb, interfering with its nutrition and growth and finally causing its distal portion to degenerate and perhaps even drop off altogether (Fig. 128, J). This process was spoken of as "amniotic amputation." Streeter (1930) studied large numbers of such cases with extreme care. His conclusion was that a focal degenerative process in the extremity itself is the primary cause. The amniotic adhesions, which undeniably do sometimes occur at the point of amputation, are regarded by Streeter as secondary. He interprets them merely as expressions of the general tendency of fibrous adhesions to form at any site where tissue destruction has left areas devoid of their normal epithelial covering.

Persistence of the Tail A well-developed tail will be remembered as one of the conspicuous characteristics of human embryos of the second month (Figs. 58-60). In the normal course of events, during the third month the tail disappears as an external feature (Figs. 106, 109). This is due in part to regressive changes in the tail itself, and in part to the concealment of what is left of the tail in the crease between the rapidly growing buttocks. Occasionally, the tail not only fails to regress but actually continues to grow in pace with the rest of the body (Fig. 130). Outside of the medical profession one is unlikely to know of the occurrence of such an anomaly because the tail can be so easily removed surgically, and the patient and the family are reluctant to admit the possession of such tangible evidence of their evolutionary history.



FIG 129 Family groups showing inheritance of developmental defects of the appendages A, Brazilian family with agenesis of hands and feet (From Streeter, after Turner) B, Syndactyly in the hands of a father, and (C, D, E) three sons (After Broman)

Gigantism and Acromegaly Gigantism appears to be due primarily to an endocrine disturbance involving excessive production of the growth-promoting hormone of the anterior lobe of the hypophysis. This hyperactivity, moreover, must begin during the growth period if true gigantism is to be the result. Its effect seems most strikingly exerted on the bony framework of the body, although other tissues must obviously keep pace with skeletal growth. When this disturbance begins early and continues throughout the growth period, individuals up to nearly nine feet in height may result (Fig 131, A). If the excess production of growth-promoting hormone does not commence until the normal growth period of the individual is partially passed, there is less striking increase in height but the hands, the feet, and the

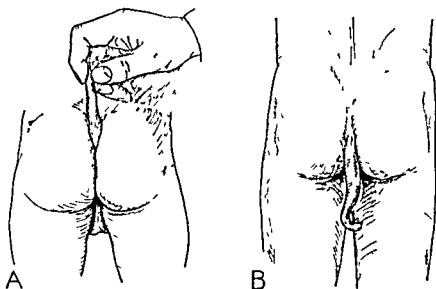


FIG 130 Two cases of the persistence of a well developed tail in human subjects A, Redrawn from a case reported by Harrison B, Redrawn from a case reported by Schultz This tail, in a 12-year-old boy, was nine inches long

jaws will undergo marked overgrowth, imparting an unmistakably characteristic appearance to the individual. The condition is known as acromegaly (akron—Greek root meaning peak or summit, and hence the derived implication, tip or extremity). Extreme cases of gigantism are commonly the sequel to hyperpituitarism which is due to a particular type of tumor (acidophile cell) of the anterior lobe of the hypophysis, so it is not surprising that such individuals are likely to die relatively young. If the afflicted person does live into adult years, skeletal changes of the acromegalic type are superimposed on the gigantism (Fig 131, B).

Dwarfism The conditions underlying dwarfism are complex and far from thoroughly understood. If we take the commonly given definition of a dwarf as "an undersized person," then there are certainly several quite different types. One type of dwarf tends to be slender and of fairly normal proportions (Fig 131, E, F). Such individuals are usually, though not invariably, poorly developed sexually and sterile. Dwarfism of this type is

believed to be attributable to conditions essentially the reverse of those producing gigantism—that is to say, there is a deficiency instead of an excess of the growth hormone of the anterior lobe of the hypophysis. The lack of sexual development, when present, is attributable to a deficiency of the gonadotropic hormones which are also formed in the anterior lobe of the hypophysis. This pituitary dwarfism may appear sporadically in apparently normal families. As far as it is possible to judge from rather inadequate records

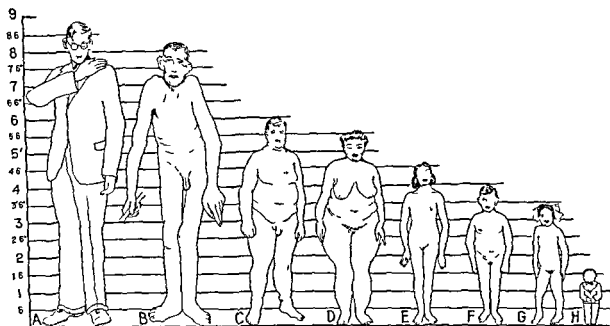


FIG 131 Examples of various disturbances of growth due to endocrine dysfunction. All the figures represent adults, drawn to the same scale.

A, Gigantism with fairly normal bodily proportions, age 19, height 8' 8" (From a photograph in *Life*, Oct 1937)

B, Gigantism, with acromegaly. Age 36 years, height 8' 3", weight 275 lbs (From Cushing "The Pituitary Body and Its Disorders")

C, Adiposogenital dystrophy in male. Age 16 years, height 6' 0", weight 275 lbs (From Babcock "A Textbook of Surgery")

D, Adiposogenital dystrophy in female (From Swale Vincent "Internal Secretion and the Ductless Glands")

E, Infantilism in a female, as a result of hypopituitarism. Age 21 years, height 4' 6", weight 67 lbs (From Engelbach "Endocrine Medicine")

F, Infantilism in a male. Age 27 years, height 4' 0" (After Bramwell)

G, Untreated myxedema. Age 29 years (From Falta "Endocrine Diseases")

H, "Midget." Age 18 years, height 1' 7", weight 12 lbs (From *Life*, 1938)

on the small proportion of such individuals capable of having offspring, the condition is not necessarily inherited.

Dwarfism of another type appears to be due to congenital deficiency of the thyroid gland. When untreated by the administration of thyroid extracts such individuals develop into *cretins*. The typical picture is that of a person of dwarfed stature and usually of rather heavy bodily proportions. The skin is excessively thick and puffy due to overdevelopment of the dermal connective tissue. This condition of the skin (myxedema) makes the lips tend to protrude and gives a generally ill-molded effect to the features (Fig 131, G). Cretins are likely to be slow of intellect and speech but are not usually sterile. It is

certain that environmental factors are important in the production of this condition, for large groups of cretins tend to appear in certain geographical districts where iodine, so necessary for the normal development and function of the thyroid gland, is markedly deficient in the ground water and hence in both drinking water and foods. That there may be also some hereditary factor involved is suggested by reports of cases of infants with defective thyroids being born to cretin parents after they had ceased to live in an iodine-poor area.

An extraordinary type of dwarf is the individual commonly known as a "midget." Such people, although of fairly normal proportions, may be as little as two feet in height. One case, featured in "Life" magazine (1937) as the smallest known adult human being, at the age of 18 years was only 19 inches tall, and weighed but 12 pounds (Fig. 131, H). Little is known concerning the underlying causes of this type of dwarfism. The individuals seem to appear sporadically as the offspring of parents of normal size. In the case illustrated, the midget's father was six feet, two inches, and his mother five feet, six inches tall, and there was no known history of dwarfism in the parents' families. There were, however, two midget sisters of the dwarf, one 22 and the other 33 inches tall.

Another type of excessively short individual ordinarily spoken of as a dwarf is the victim of a condition known as chondrodystrophy, or achondroplasia. It would perhaps be more accurate not to regard such persons as dwarfs, for their trunk is of perfectly normal size, their shortness being due entirely to the shortness of the long bones of the appendages (Fig. 178). This condition, which will be referred to again in connection with the development of the skeletal system, is definitely hereditary.

Adiposogenital Dystrophy A disturbance of body proportions which involves excessive accumulations of fat rather than any abnormality of height is known as adiposogenital dystrophy (Fig. 131, C, D). The underlying difficulty in this condition is attributable to the anterior lobe of the hypophysis. Among other things, there is a deficiency in the gonadotropic hormones, so there is poor sexual development. Thyroid function may also be at a low level. This, together with the hypogonadism, is involved in the poor efficiency of fat oxidation and the resultant gross excess of its accumulation in the fat depots of the body.

Gross Distortions of Body as a Whole Occasionally, one sees embryos which are grossly malformed both as to external configuration and internal structure. They give one the impression that the whole complex mechanism of growth and differentiation has been hopelessly upset. Under such circumstances, by the time their feeble and distorted development runs its course they may show all sorts of grotesque conditions (Fig. 132). Fortunately, such embryos, almost without exception, fail to become viable and are aborted. The knowledge that in many instances a spontaneous abortion is protection against the birth of a defective infant may be very useful to a physician in dealing with a disappointed patient.

Causative Factors in Abnormal Development It is disconcerting for a physician—or an embryologist—to be asked by distressed parents for the cause of some particular type of anomaly with which their child is afflicted. Even more troublesome is the pertinent question that is sure to follow as to whether

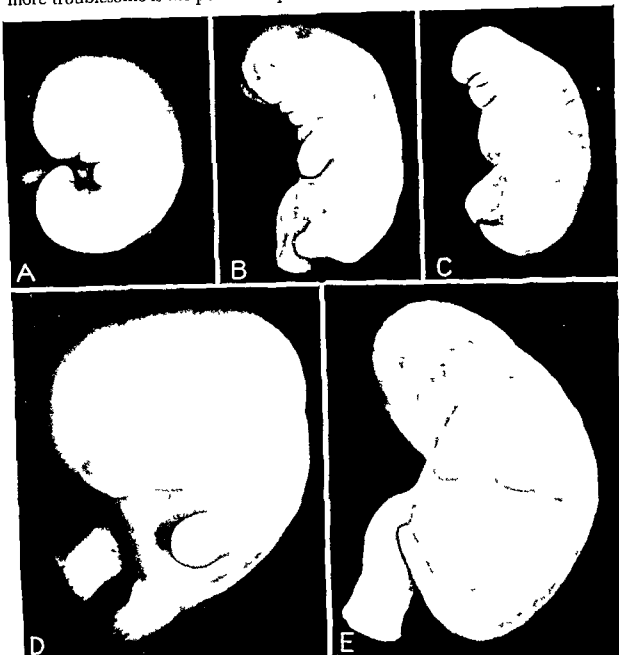


FIG 132 Five stunted and poorly molded ("cylindrical") embryos. A, University of Michigan Coll, EH 303, C-R, 3 mm. B, After Mall and Meyer, Carnegie Coll, 2173, C-R, about 12 mm. C, After Mall and Meyer, Carnegie Coll, 2222, C-R, about 4.5 mm. D, University of Michigan Coll, EH 144, tubal pregnancy, C-R, 13.5 mm. E, After Mall and Meyer, Carnegie Coll, 885, C-R, about 9.5 mm.

or not the same thing is likely to happen in another pregnancy. Too frequently, under such circumstances, we are far from sure that we know the correct answers. As is the case in most baffling situations, those who know least are likely to talk with the most assurance. Without doubt, this has been so ever since man became vocal, and in all the intervening years the number and

variety of "explanations" for malformations that have been advanced without any basis in fact are truly astonishing. They range all the way from such naïve animistic conceptions as that of Pliny that "Nature creates monsters for the purpose of astonishing us and amusing herself," to fantastic alleged causes like intercourse during the menstrual period. The Roman god Vulcan was supposed to owe his deformity to Juno's violation of the taboo surrounding this period. Even intercourse with animals has been said to be responsible for the production of monsters. The Centaurs of Greek mythology were supposed to have so arisen. Interesting as are the superstitions and the folklore attaching to this as to all phases of childbearing, it would carry us too far afield to dwell here on such matters.

There is, however, a belief in the effect of what is spoken of as "*maternal impressions*," or "*prenatal influence*," which belongs in the folklore category but, nevertheless, is still sufficiently widely credited among lay persons to call for comment. It is astonishing how many people believe that a fright or an unpleasant sight during pregnancy will cause a child to be "marked" in a manner suggesting the incident. This is, of course, utterly groundless, but even a careful explanation that the molding of the external ear takes place during the seventh to the tenth week will not always convince a woman steeped in old wives' tales that the malformed left ear of her infant son really could not have been caused by the fright she got in the sixth month of her pregnancy when she was held up and robbed by a man with a cauliflower ear. Part of the difficulty of convincing the woman, it must be admitted, lies in the fact that we are not able to offer with conviction a simple and readily understandable explanation to take the place of her unscientific but emotionally satisfying one.

In dealing with the causative factors involved in developmental malformations, most of our discussion must be guardedly tentative. It is true that we now know many things that can be ruled out but we are realizing with increasing clearness that no simple blanket explanation is adequate to cover the astonishing variety of cases encountered, and that each type of defect must be studied intensively and separately. From such studies we are at least beginning to know the directions in which we must seek the underlying causes. As in so many other instances, we come back again from still another angle to that basic problem of the interplay of heredity and environment. Beyond a doubt, both are involved in the causation of anomalous development, but any generalizations as to their relative importance are unwise because in different anomalous conditions the causative factors vary. All the possibilities must be carefully scrutinized for the specific case under consideration. Certain malformations, such as some of those of the extremities we have just considered (Fig 129), are inherited with a regularity that suggests a dominant character perhaps dependent on a gene defect which originated as a mutation. A similar situation seems to exist with other conditions such as the long-bone defects of achondroplasia (Fig 178).

There are many other malformations in which heredity would seem to be

implicated but in a manner much less easy to follow. Such defects, for example, as cleft lip and cleft palate (Fig 253) on the basis of present evidence appear to be inherited in the manner of a Mendelian recessive character. This, of course, means that the defect might be carried in the germ plasm of an apparently normal individual until a mating occurred with another person with the same latent defect. Even with rapidly breeding laboratory animals under controlled conditions, it is no simple matter to determine the exact manner in which such recessive characters are transmitted. When one takes into consideration the facts (1) that data for the genetic study of man have been collected for only a comparatively brief period, (2) that human germ plasm is appallingly heterozygous in comparison with the purity of line demanded by any animal breeder, and (3) that it is not feasible to set up specific matings to satisfy our scientific curiosity, it does not seem surprising that we have made such slow progress in unraveling the transmission of recessive traits. Much more extensive and more carefully kept records must be available before the more intricate of the hereditary problems can be faced with assurance. But this should not make us unwilling to take constructive action toward stopping the hereditary stream of such defects as we already know to be directly inheritable.

Specific and readily recognized traits are by no means the only ones carried by heredity. Subtle differences in the vitality of the fertilized egg are transmitted to it through the germ plasm. Some families are conspicuously long-lived and others tend to early death. We are so familiar with these hereditary differences in longevity that it seems trite to mention them, nevertheless it is often overlooked that this sort of difference reaches back into embryonic life. An egg capable of responding to fertilization may develop for only a short time because of a hereditary lack of normal vigor, or lack of the normal capacity for differentiation. With somewhat nearer normal vigor of growth and differentiation there may be the lack of adequate regulation of the function of some of the growing tissues, as, for example, excess production of the growth hormone by a hyperactive anterior lobe of the pituitary, or deficient production of thyroid hormone. Such disturbances in the regulation of the activity of one organ, in turn, cause the structural abnormalities of other organs, for development is a progressively constructive process which can not be disturbed at one point without bringing consequential changes at a whole series of others.

The disturbances we have just been considering are of the so-called intrinsic type. That is to say, they operate from within the embryo itself, and as far as we know anything about their ultimate origin we would have to attribute them to something wrong with what the embryo received by heredity. This is by no means the only way in which developmental defects may be caused. There is abundant experimental evidence from animal material that abnormalities may be produced by modifying the environment. The variety of mechanical, physical, and chemical means which may be effectively employed is surprising. Mechanical separation of blastomeres as an artificial

means of producing twins in certain of the lower forms has already been mentioned. The start at least of double heart formation may be induced by exerting pressure between the paired cardiac primordia at the time they should normally be fusing (Goss, 1935).

Although direct injury or continued pressure can cause a variety of defects in the embryos of lower animals developing outside the body of the mother, the sheltered intra-uterine habitat of the human embryo greatly reduces the likelihood of mechanical injuries playing any significant rôle in the causation of its anomalies. The most frequently cited examples of malformations caused by mechanical damage in man have been the so-called amniotic amputations. As we have seen, Streeter's recent study of such conditions indicates that the primary cause is a local necrosis and that such amniotic adhesions as may be seen are secondary and not causative. The protection afforded by the abdominal and uterine walls, together with the cushioning action of the amniotic fluid, makes the traumatic injury of the human embryo through falls or blows very unlikely. When such accidents lead to abortion, it is rather through hemorrhage at the site of placental attachment than through direct injury to the embryo itself.

Physical factors which have been found to be involved in the production of anomalies in experimental work with animals are temperature changes and radiation. The dropping of the temperature to levels where growth is seriously slowed, or stopped altogether, followed by return to normal incubation temperatures, produces a high incidence of abnormalities in the eggs of birds. In a number of forms, including some of the mammals, irradiation with sublethal doses of x-rays or radium emanations has been reported to cause anomalous development. The observations on temperature changes are probably of purely theoretical interest as far as human development is concerned, for it seems exceedingly unlikely that any temperature changes of sufficient magnitude to affect the embryo occur within the uterus. With the extent to which x-rays are being used in modern medical practice, it would be pertinent to know much more than we now do about their effect on development, although there seems no reason to believe that any danger of causing malformations is involved in their use at the intensities commonly employed in clinical work.

Change in the relative amount of various chemicals usually present in sea water causes the production of anomalies of several different types in fish embryos. An insufficient amount of oxygen has similar effects on a wide variety of forms. Recently, Warkany and his co-workers have shown in a brilliant series of studies on rat embryos that skeletal defects may be caused in offspring by feeding defective diets to the mothers. Moreover, the malformations apparently do not occur in merely haphazard fashion but their nature may be predicted to a certain extent on the basis of the specific vitamin fraction withheld.

A conception of very great theoretical importance was put forward by Stockard as a result of his classic experiments with the common marine min-

now, *Fundulus*. He noticed that different disturbances applied at the same phase of development would tend to produce the same defects, whereas the same disturbing factor applied at different phases of development produced different defects. On further analysis, the effect that all the disturbing agents seemed to have in common was the power of slowing or stopping growth. Any effective treatment—whether it was a drop in temperature, a lowering of oxygen supply, or a deleterious alteration of the balance of the salts in the sea water—would exert this retarding action most strongly on whatever developmental process happened to be in a rapidly changing phase at the moment the treatment was applied. That there are such accelerated phases in the development of each of the organ systems is well known. For example, there is the period of tremendously rapid change for the central nervous system when it is being transformed from a thickened axial plate into an internally placed tube. According to Stockard's conception, anomalies of the central nervous system would be produced by any sort of disturbing influence operative at this critical period in its molding. Other organ systems growing more slowly would be unaffected. However, let any one of these growth-disturbing factors become operative at some other time, when another organ was in a critical phase, and that organ would be the one that showed defective development. According to Stockard's conception, the inhibiting action does not need to last long, for the center of accelerated activity shifts from one organ to another as development progresses, and if an organ fails to "take its tide at the full" and differentiate at the time of its transient metabolic dominance, it never can carry out fully the critical changes which should then have been culminated.

Stockard's interpretation seems to explain satisfactorily a great many otherwise puzzling results of experimental disturbances of environmental conditions. It would appear, however, that there has been a little tendency for people to be swept off their feet by the seeming simplicity of the explanation and the brilliance of the work that led to its advancement. As we shall see later, when certain developmental defects of the nervous system and of the heart are discussed, the abnormal conditions which appear are far more varied than can possibly be accounted for on the basis of a mere cessation or retardation somewhere along the course of normal development. There are certainly many anomalies which can most readily be so explained, but there are others which are due to such widely divergent processes as growth which has gone too far, resorption which has gone too far, resorption which has not gone far enough, or growth fairly normal in amount but abnormal in location. Such radical differences in the immediate mechanisms concerned should give us pause in considering any "blanket explanation" of congenital defects. Certainly the ultimate solution of the intricate problem of their causation will not be advanced by overemphasizing the developmental-arrest concept when congenital defects may equally possibly be the result of a resorptive process which has gone astray, or a growth process which has failed to stop soon enough. Pending the acquisition of more satisfactory knowledge as to

means of producing twins in certain of the lower forms has already been mentioned. The start at least of double heart formation may be induced by exerting pressure between the paired cardiac primordia at the time they should normally be fusing (Goss, 1935).

Although direct injury or continued pressure can cause a variety of defects in the embryos of lower animals developing outside the body of the mother, the sheltered intra-uterine habitat of the human embryo greatly reduces the likelihood of mechanical injuries playing any significant rôle in the causation of its anomalies. The most frequently cited examples of malformations caused by mechanical damage in man have been the so-called amniotic amputations. As we have seen, Streeter's recent study of such conditions indicates that the primary cause is a local necrosis and that such amniotic adhesions as may be seen are secondary and not causative. The protection afforded by the abdominal and uterine walls, together with the cushioning action of the amniotic fluid, makes the traumatic injury of the human embryo through falls or blows very unlikely. When such accidents lead to abortion, it is rather through hemorrhage at the site of placental attachment than through direct injury to the embryo itself.

Physical factors which have been found to be involved in the production of anomalies in experimental work with animals are temperature changes and radiation. The dropping of the temperature to levels where growth is seriously slowed, or stopped altogether, followed by return to normal incubation temperatures, produces a high incidence of abnormalities in the eggs of birds. In a number of forms, including some of the mammals, irradiation with sublethal doses of x-rays or radium emanations has been reported to cause anomalous development. The observations on temperature changes are probably of purely theoretical interest as far as human development is concerned, for it seems exceedingly unlikely that any temperature changes of sufficient magnitude to affect the embryo occur within the uterus. With the extent to which x-rays are being used in modern medical practice, it would be pertinent to know much more than we now do about their effect on development, although there seems no reason to believe that any danger of causing malformations is involved in their use at the intensities commonly employed in clinical work.

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etiology, we would be on sounder ground if we were more restrained in our use of "developmental arrest" with its often false implications as to causation, and employed some such noncommittal expression as developmental distortion or developmental defect.

The causation of anomalies can not be discussed without at least a passing word of comment on the possible rôle played by disease. In the past, much emphasis has been placed on intra-uterine syphilis as a cause of malformations. Of its damaging effect on the infant there can be no doubt, but this damage seems to be the specific and direct effect of the disease rather than any tendency for the disease to cause developmental processes to become abnormal. Of course, if an extensive syphilitic lesion happens to destroy a growing area, there is an abnormality at that point, but it would seem more logical to regard this as a manifestation of the disease rather than as a developmental disturbance.

The possible causative effect of uterine disease or faulty placental attachment in the production of anomalies needs much more critical study. There are many workers whose opinion must be respected who feel that disease of the uterus or placenta can so disturb the normal environment of the mammalian embryo that it brings into play chemical disturbances and oxygen deficiencies of precisely the type that experimentation with lower animals has shown to be so effective in causing anomalies. Much more work is needed before one could step into this controversy with any assurance. There is, as yet, no way of telling by studying an aborted abnormal embryo whether it came from an egg poorly endowed by heredity so that it formed a faulty uterine attachment because of a lack in its own intrinsic power of differentiating effective extra-embryonic membranes, or whether it was a well endowed egg that failed to form a good uterine attachment because the uterine mucosa did not respond properly to the presence of a normal chorion. As for the embryo itself, its badly molded body might be attributed to the same germinal defect that caused it to form membranes incapable of a good attachment, or with equal reason to a poor attachment causing an oxygen deficiency which in turn interfered with the development of what was potentially a perfectly normal egg. Under the circumstances, progress toward a real understanding of these problems will best be furthered by keeping our minds open to all the possibilities and alert for further trustworthy evidence.

9

Integumentary System

THE SKIN

The skin of the adult is double-layered, consisting of an outer layer of stratified squamous epithelium called the epidermis, and a deeper layer of fibro-elastic connective tissue known as the dermis or the corium. The epidermis is of ectodermal origin and the corium arises from the mesoderm.

The Epidermis The superficial ectoderm of embryos during the first, and into the beginning of the second month, is a simple cuboidal epithelium with the nuclei lying closely packed (Fig 133, A). About the middle of the second month, some of the cells begin to be crowded to the surface, forming a thin layer of flattened cells known as the periderm (Fig 133, B). The periderm is called by many writers the epitrichial layer of the epidermis because the hairs which later grow up from the deeper layers are said not to penetrate this thin surface layer but to push it up on their growing tips, causing it to be cast off if it has not already disappeared.

During the latter part of the second month, there is a tendency for the epithelium to become thicker. This is manifested at first by a staggering of the nuclei (Fig 133, C) presaging the beginning of cell rearrangement which leads rapidly to the formation of an intermediate layer between the flattened cells of the epitrichial layer and the basal layer adjacent to the underlying dermis. The cells of this intermediate layer tend to become enlarged and show a high degree of vacuolation (Fig 133, D, E).

During the third month, the deep-lying layer of cells becomes sharply distinct from the rest of the epithelium. These cells are said to constitute the germinative layer (*stratum germinativum*) because they are the ones which undergo the repeated cell divisions responsible for the growth of the epidermis. The cells of this layer show a dense, strongly staining cytoplasm and well-marked cell boundaries (Fig 133, F, G).

During the fourth month, the epithelium starts to become many cell layers thick and to approach its definitive structure. The cells in the zones overlying the germinative layer begin to show indications of the accumulation of keratin. It is the presence of this keratin which gives the characteristic toughness to the superficial layers of cells which constitute the *stratum corneum* of the epidermis.

In such areas as the palms of the hands and the soles of the feet, where the skin is subjected to more than ordinary wear, the keratinization of the outer

layer is much heavier than it is in the general body surface. Interestingly enough, the greater thickness of palmar and plantar epidermis becomes evident in the embryo long before it is possible for these areas to have been subjected to any more wear than other parts of the skin. In these areas, the epidermis is not only more cell layers thick but there is evident also a more marked differentiation of its layers. Starting from the basement membrane

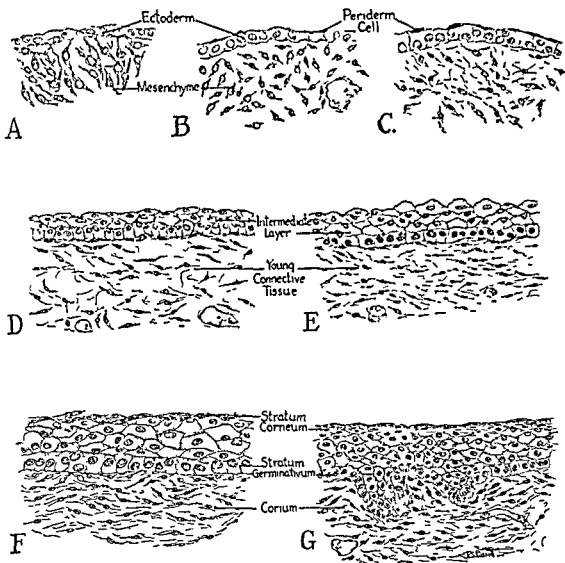


FIG 133 Projection drawings ($\times 300$) showing some of the stages in the histogenesis of the skin. All drawings were made from reasonably comparable areas of the skin of the back. A, At 2.1 mm. B, At 9 mm. C, At 16 mm. D, At 32 mm. E, At 60 mm. F, At 85 mm. G, At 145 mm.

toward the surface, one can recognize (1) the germinative layer, (2) the granular layer, (3) the lucid layer, and finally (4) the thick keratinized layer. With the exception of the deeper strata, the peculiar staining reactions which make these layers stand out from one another are correlated with the production of the keratin which is so characteristic a feature of this particular type of epithelium. The minute darkly staining particles which characterize the granular layer are composed of a precursor substance, keratohyalin. The lucid

layer contains a material which is believed to represent keratohyalin granules which have undergone a chemical modification involving their softening and fusion into a homogeneous semifluid condition. This substance, known as eleidin, stains brilliantly with the acid dyes such as eosin so when it is present in any quantity it is readily demonstrable. The outermost layer is made up of closely packed flattened cells heavily impregnated with fully elaborated keratin. As the keratin accumulates in these cells, they become more and more sluggish, and finally die so that the surface layer of the epidermis is made up of tough, scale-like, dead cells and is resistant both to abrasion and to the ready passage of fluids.

The Dermis The dermis or corium when it is fully developed, consists of a closely woven layer of fibro-elastic connective tissue immediately underlying the epidermis. This connective tissue arises from wandering mesodermal cells of the type collectively designated as mesenchyme. As was pointed out when the differentiation of somites was being discussed, it was formerly believed that the mesenchymal cells forming the dermis came from the ventrolateral part of the somite which for that reason was named the dermatome (Fig. 63). While some cells do migrate out from this part of the somite and contribute to the formation of the deep layers of the skin, most of them are concerned in the formation of muscle. The dermis arises from mesenchymal cells which migrate out from whatever mesodermal areas are nearest and then arrange themselves in a zone beneath the ectoderm. The steps by which the mesenchyme becomes converted into connective tissue are the same in the case of the dermis as for the fibrous connective tissues in general (See Chapter 10).

In the early stages of the formation of the skin, the plane of union between the epithelium and the dermal connective tissue is smooth (Fig. 133, A-F). During the fourth month, however, as the epithelium thickens, its lower surface becomes irregular, exhibiting ridges and hollows into which the connective tissue pushes. In the palms and soles, by the sixth month, these irregularities begin to show on the surface in the extraordinarily intricate and highly individualistic patterns recorded in finger printing. In addition to these ridges of the palmar and plantar areas, the skin in general is beset with local elevations of the corium which extend into minute pits in the under surface of the epithelium. Connective-tissue projections of this type are called dermal papillae. They contain the terminal loops of the capillaries nourishing the skin and some of them have, in addition, the characteristic Meissner's corpuscles which are the sensory nerve end-organs of touch (Fig. 228, I).

NAILS AND HAIR

The Nails Our finger- and toenails are epidermal specializations which are homologous with the claws of lower animals. The spots where nails will develop are suggested by the molding of the tips of the digits by the middle of the third month of intra-uterine life. The nail itself is foreshadowed by a thickened plaque of epithelium known as the primary nail field. As this area

enlarges, it sinks down into the dorsal surface of the tip of the digit and is bounded laterally and proximally by an elevated fold of epidermis (Fig 134, A) As its growth progresses, the nail field soon undercuts the surrounding

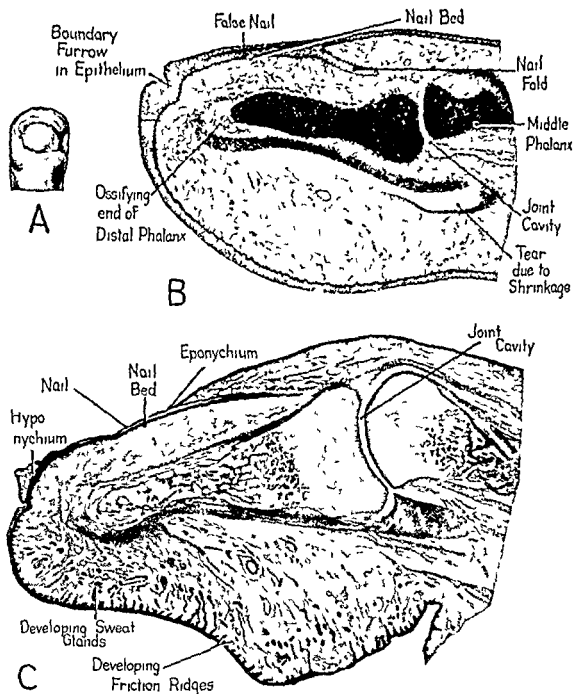


FIG 134 Development of fingernail A, Section of fingertip of a 40-mm human embryo ($\times 15$) (After Kollmann) B, Section of fingertip of a 140-mm human embryo ($\times 50$) (After Fischel) C, Section of fingertip of a 320-mm human fetus ($\times 25$) (After Fischel)

elevated areas to form the nail folds (Fig 134, B) At the same time, there is some local keratinization in its central area to form the so-called false nail The material of the true nail develops at a later stage from the undertucked epithelium of the nail fold and the proximal part of the nail bed in the region

of the lunula (Fig 134, C) The nail thus grows forward from its base in a manner quite familiar to anyone who has lost a nail as a sequel to pounding his finger In the slow growth of the nails during fetal life, it takes until the final month of gestation before they reach the tips of the digits, and even then the distal part of the nail is still very thin and soft

Although the nails are formed by a process that is clearly some kind of modification of the keratinization which goes on in the epidermis as a whole, the details are not as yet well understood Some regard the nail substance as a special form of eleidin Others contend that it is made up of specialized keratin fibrils which have been formed and matted together without going through a keratohyalin and eleidin stage as in the usual process of keratinization (Hoepke, 1927) During the early part of its development, a thin keratinized layer continuous with that of the surrounding epidermis completely covers the nail By the latter part of fetal life, only the marginal portions of this so-called eponychial layer persist and adhere to the nail plate Particularly around the proximal margins of the nail this tendency for the eponychial layer to adhere persists throughout life, to the annoyance of mere males and the profit of manicurists

The Hair Long before any hair shafts appear, local down-growths into the underlying connective tissue from the germinative layer of the epidermis mark the points at which hair and sebaceous glands are starting to develop (Fig 135, A) The precise time at which these primordial hair follicles make their appearance differs in different cutaneous areas They become recognizable on the eyebrows, eyelids, lips, chin, and scalp during the third month In the skin of the general body surface they are about a month later in making their appearance

Once one of these primordial follicles starts to grow down into the underlying connective tissue, it differentiates rapidly Its deep end then becomes enlarged to form the bulb of the hair This bulb soon becomes molded into a shape suggestive of an inverted cup into which there pushes a highly vascular concentration of connective tissue called the papilla (Fig 135, C) On the lower side of the obliquely directed follicle there appear two swellings The upper one of these is the primordium of a *sebaceous gland*—one of those small glands destined to discharge its oily secretion to the skin surface indirectly by way of the hair follicle The lower swelling, called the epithelial bed, is a region of rapid cell proliferation especially conspicuous when the hair follicle is rapidly growing (Fig 135, C)

The hair itself is a column of keratinized cells arising from the basal cells of the epithelial bulb lying adjacent to the vascular papilla As it grows, the hair shaft pushes toward the surface by making an opening for itself through the center of the original cylindrical epithelial ingrowth, the cells of which thus come to surround the growing hair shaft and constitute its epithelial sheath (Fig 135, C, D) Meanwhile, the developing connective tissue of the dermis has been concentrating about the follicle to form a fibrous sheath investing the hair and its epithelial sheath It is in this fibrous sheath, just below the

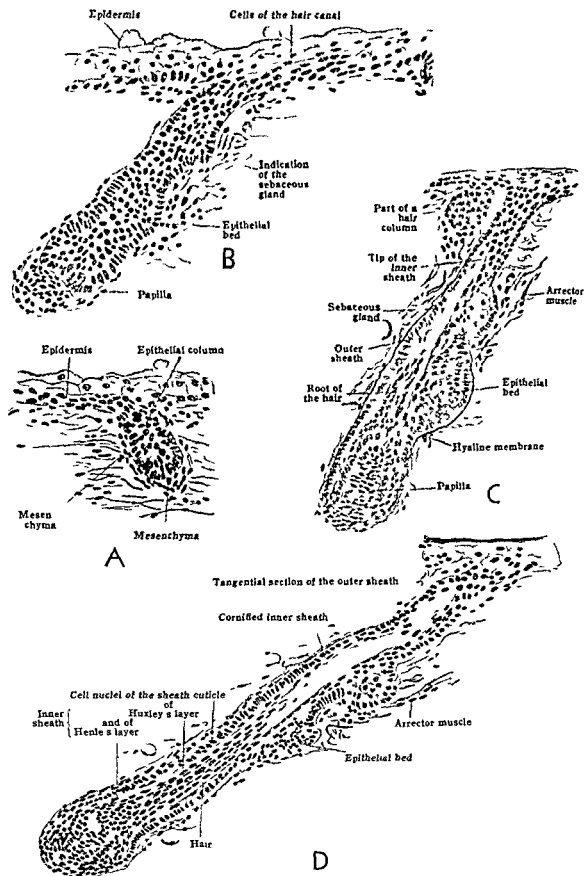


FIG 135 Sections ($\times 230$) showing four stages in the development of hair follicles as seen in a human embryo of the fifth and sixth months (From Bremer-Weatherford "Text-book of Histology")

level of the sebaceous glands, that a tiny strand of involuntary muscle is attached to each hair follicle. These minute muscles, because they pull the hair follicle into a less oblique position and thereby make the hair stand more vertically, are called the *arrector pili muscles*. We are quite familiar with the results of their action in the bristling hair along the shoulders and spine of a dog becoming belligerent. Another example is the erection of the hair of long-haired animals as a response to cold—a reaction which thickens the zone of insulation provided by the air spaces among the hairs. Although our own body hairs are too few and too fine to give us any appreciable amount of warmth, we still can see the evidences of the same primitive reaction on our chilled skin in the tiny elevations (“goose pimples,” “ducky bumps”) caused by the contraction of these muscles futilely pulling up rudimentary hairs.

It is usually toward the end of the sixth or the beginning of the seventh month before hairs begin to be visible at the surface. The first hairs to emerge are very slender and close together so that they constitute a characteristic downy coat on the fetus known as the lanugo. The lanugo is usually most conspicuous during the seventh and eighth months. It then begins to be shed, most of these first hairs being lost by the time of birth or very soon thereafter. The replacing hairs are believed to be developed at least in part from new follicles. Certainly their distribution does not correspond to the distribution of the lanugo hairs. Throughout life, hair is shed and regenerated. At the end of its cycle, a hair root is carried upward as the follicle undergoes regression. It is finally cast off, following which the follicle, under favorable circumstances, may begin to form a new hair.

In the succession of hair crops, the character of the replacing hair in some regions shows little change, whereas in other regions the changes are striking. In females, the face, neck, and trunk show replacing hairs little different from the lanugo. In the male the areas which remain fine-haired are less extensive. In such specialized locations as the eyebrows, eyelashes, and scalp, the replacing hairs tend to become slowly and progressively heavier until their adult thickness is attained. Under the influence of the sex hormones the changes in the character of the pubic and axillary hair in both sexes, and of the beard and the hair of the extensor surfaces of the forearms and the ventral surfaces of the trunk in the male, are accomplished very rapidly at the time of puberty.

GLANDS OF THE SKIN

Sebaceous Glands As was mentioned in connection with hair formation, the primordia of the sebaceous glands make their appearance as buds of cells arising from the sides of hair follicles (Fig. 135, B, C). The initial bud rapidly develops into a saccular and lobulated secreting portion which discharges through a narrowed duct into the hair follicle about two-thirds to three-fourths of the way up from the bulb to the surface. The oily material produced by the gland accumulates as large numbers of minute droplets within the cytoplasm of the cells of the secreting areas. When the central cells of an

acinus have become fully loaded with these droplets they break down and cell remnants and oily secretion together are discharged from the gland. This type of secretion is called holocrine (i.e., the whole secretory cell laden with its characteristic product passes off as the secretion). The material thus produced in the sebaceous glands is responsible for the natural oiliness of the adult hair and skin. Before birth it is the chief constituent of the whitish, cheesy material (*vernix caseosa*) found on the skin surface of older fetuses.

While sebaceous glands are thus ordinarily associated with the hair, they appear in certain locations such as the vulva, the anal canal, and the deeper parts of the nasal vestibule where there is no hair. All these areas are ones where infolding of ectoderm occurs during development, and what seems to have happened is that the primordial hair follicles, when they were infolded, did not produce hairs but did bud off sebaceous glands which differentiated independently. In the anal and preputial regions of certain animals these modified sebaceous glands and also some especially large sweat glands become very highly developed, producing strongly scented material, the odor of which may be defensive (skunk) or may have a secondary sexual significance (musk deer). The scent-carrying properties of some of these oily secretions has led to their extensive use as bases for commercial perfumes.

Sweat Glands The primordial epithelial buds destined to form sweat (sudoriferous) glands begin to make their appearance on the palmar and plantar surfaces during the fourth month. In other cutaneous areas they are a little later in developing. As is the case with glands in general, the initial down-growth from the germinative layer of the epithelium into the underlying connective tissue is in the form of a solid cylindroid mass of cells. These cell cords continue to extend until, during the sixth month, their deep ends have reached the loosely woven and fat-containing subcutaneous connective tissue which underlies the more densely woven fibers of the dermis. When this depth has been reached the distal end of the cell cord coils freely to attain the characteristic form of the adult glands. Usually by the seventh month the cell cords hollow out to establish lumina but, according to Windle, actual secretory activity until after birth is probably negligible.

Mammary Glands The first visible epithelial differentiation leading toward the formation of the mammary glands is recognizable in embryos during the second month of development. This is surprisingly early in view of the fact that the mammary glands are structures which appear late in phylogeny and which do not go into functional activity in the individual for many years after birth. It is usually during the sixth week of development that a pair of bandlike thickenings make their appearance along the ventrolateral body-walls from the axillary to the inguinal regions. The location and extent of these so-called "milk lines" is indicated schematically for mammals in general in Fig. 136, A. It is from the epithelium along the course of the milk lines that the mammary glands arise. Different anteroposterior levels of the potentially mammary-gland-forming tissue are capitalized in different species. Some animals (for example, the sow and the bitch) develop a series of nipples

spread over nearly the entire length of the milk line. In the fruit bats and flying lemurs mammary glands are developed in the axillary region, whereas in some of the cetaceans the nipples develop in the inguinal region almost on the labia majora. In the human species the different height at which the breasts are developed in different racial groups is indicative of the utilization of slightly different levels of the milk line in their development. Normally this variation occurs within rather narrow limits of the pectoral region, but not infrequently supernumerary nipples may occur at other levels along the course of the milk line (Fig 136, B)

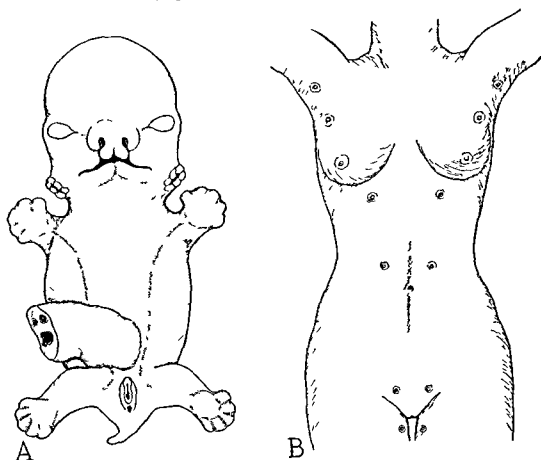


FIG 136 Schematic diagrams showing in A, the position of the "milk line" in mammalian embryos in general, and in B, the commonest sites at which supernumerary nipples and mammary glands occur in women

In histological sections, the milk line appears as a bandlike thickening of the ectoderm (Fig 137, A). With the continuation of locally accelerated cell division the epithelial thickening begins to push downward into the underlying connective tissue. By the eighth week of development, the milk line as a whole is very difficult to follow, but at the point where mammary glands are starting to form a lenticular mass of epithelial cells can be seen extending deeply into the underlying mesenchyme (Fig 137, B). During the third month, the primordial cell masses which are destined to give rise to the mammary glands grow slowly without showing much differentiation (Fig 137, C). During the fourth month, cords of cells begin to bud off in various directions into the surrounding connective tissue (Fig 137, D). These cell cords are destined to

form the lining of the main ducts, and the terminal cell clusters at the ends of the cords will later branch and rebranch to form the smaller ducts and the secretory acini of the gland

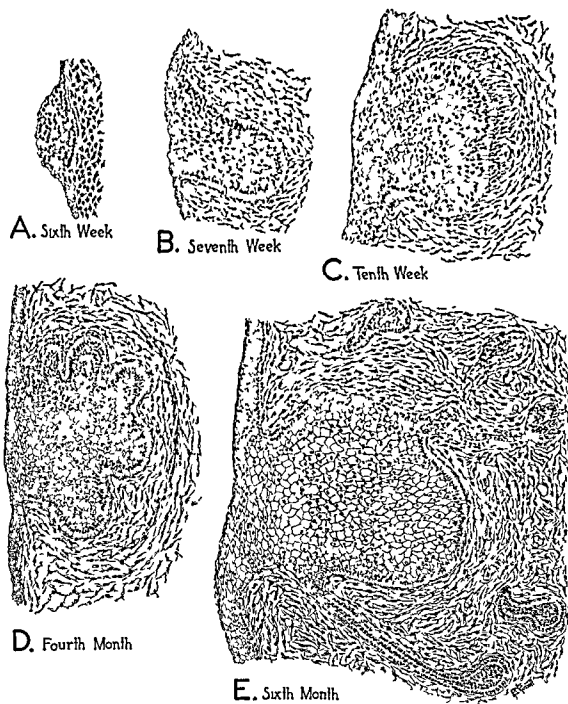


FIG 137 Stages in histogenesis of mammary glands Projection drawings ($\times 150$) A, At 11 mm B, At 17 mm C, At 48 mm D, At 100 mm E, At 200 mm

The growth of this system is, however, very slow and by the time of birth only the main ducts have taken shape (Fig 138) At this time there is no evident difference in the mammary-gland development in the two sexes In the male, the glands do not advance appreciably beyond their infantile

condition In the female, there is little change until puberty approaches, when there begins a rapid increase in the size of the breasts (Fig 139) Most of the molding of the breast, however, is due to the accumulation of fat There are gradual extensions of the primordial epithelial cords at the time of puberty, but the actual bulk of this potentially secretory system still constitutes an exceedingly small proportion of breast tissue Not until pregnancy occurs

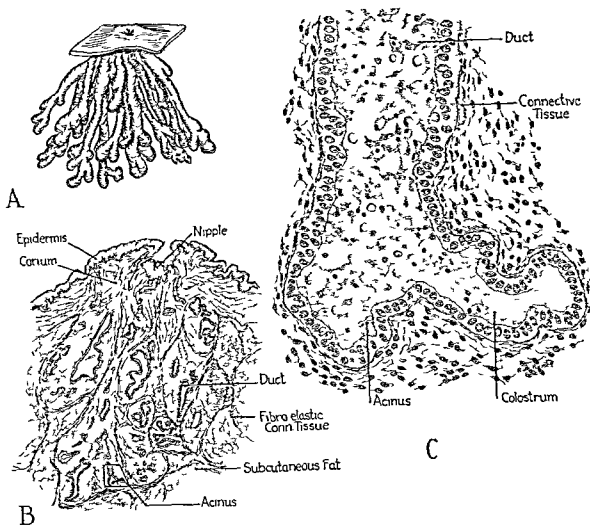


FIG 138 Mammary gland of the fetus in the latter part of pregnancy A, Reconstruction of the ingrowing epithelial cords in a fetus of six months, $\times 10$ (After Broman and Lustig) B, Section through mammary gland and nipple in a term fetus, $\times 12$ The area within the polygon is shown enlarged in C C, Projection drawing, $\times 300$, of a single acinus

does the glandular tissue show any indication of the tremendous development of which it is capable Then under hormonal stimulation its growth and differentiation become exceedingly rapid Visible enlargement of the breasts begins to be noticeable after the second month The nipples also increase in size and the areolae around them become larger and more pigmented The greatest part of the extension of the duct system has been accomplished in the first two-thirds of the period of gestation During the last third of gestation the changes involve more particularly the differentiation of the acini leading toward their secretory activity For the first two or three days after birth the

form the lining of the main ducts, and the terminal cell clusters at the ends of the cords will later branch and rebranch to form the smaller ducts and the secretory acini of the gland

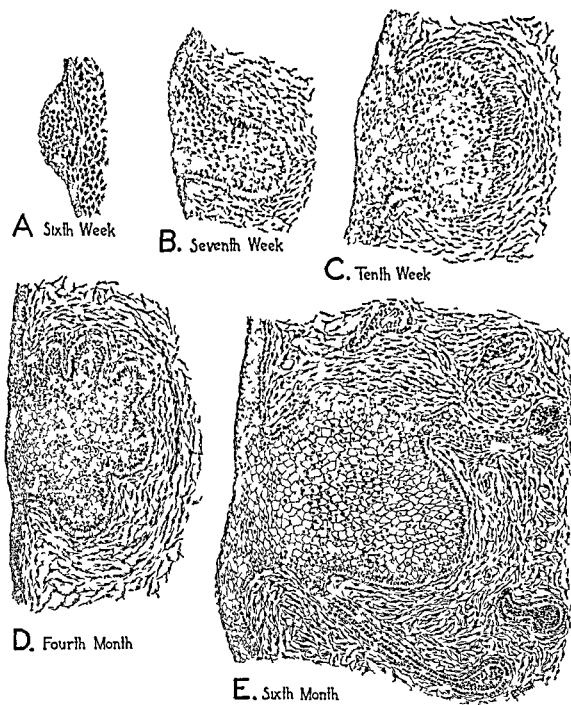


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in small elevated areas of the skin (pigmented moles) These pigmented moles have a tendency, when irritated, to change into a highly malignant type of neoplasm known to pathologists as a melanoblastoma Home or beauty parlor tampering with them is exceedingly dangerous They should be closely watched and if there is any suspicion of increase in size or of their becoming irritated, a thoroughly competent surgeon should immediately be consulted with a view to their removal

Angiomata The strongly colored birthmarks of the type commonly called "port wine spots" are due not to any unusual pigmentation of the epidermis but to the showing through of abnormally rich plexuses of blood vessels in the dermis Their color varies from red to purplish, according to the degree of stasis in the tortuous closely woven small channels constituting the angioma



FIG 140 Two cases of ichthyosis (Courtesy, Dr Arthur C Curtis)

Polymastia and Polythelia The occurrence of supernumerary breasts which contain actual mammary gland tissue is known as polymastia In distinction, the term polythelia is used to cover a similar condition in which only the nipples have been formed In the great majority of cases the extra breasts or nipples tend to appear as one would expect along the normal course of the milk line (Fig 136) Nevertheless, sporadic cases occur in both sexes in which the breasts or nipples are developed from cutaneous areas not normally involved in mammary gland formation in any known species of animal—adult or embryonic The composite diagrams of Fig 141 indicating all the locations at which aberrant mammary glands or nipples have been reported clearly show the wide departures from the conventional positions along the milk line that can occur The distribution is suggestive of that of Job's ubiquitous boils Such sporadic appearances of structures at locations which are not explicable on the basis of normal developmental patterns further emphasize the difficulties of "explaining" all anomalies on the developmental arrest concept

Gynecomastia In certain rare instances a male individual has been known to develop breasts of female type (Fig 142) The condition, known as

mammary secretion is a thin yellowish fluid called colostrum. About the third day postpartum the fat content of the secretion rises abruptly and it becomes typical milk.

An interesting sidelight on the powerful effect of the hormones bringing the breasts into activity during pregnancy is afforded by the production of so-called "witches' milk" by the mammary glands of newborn infants of either sex. This quite usual occurrence is apparently due to the stimulating effect of hormones from the maternal blood stream which have crossed the

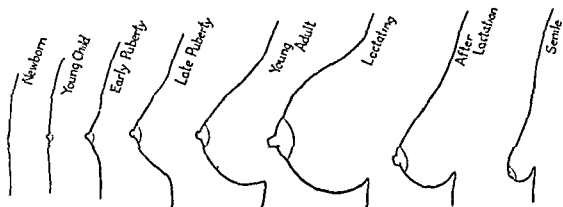


FIG. 139 Profile diagrams indicating characteristic changes in configuration of breasts at different ages and with functional activity

placental barrier to become active in the fetus. Sections of the swollen terminal portions of the mammary ducts at this time show an accumulation of colostrum-like material (Fig. 138, C).

DEVELOPMENTAL ABNORMALITIES OF INTEGUMENTARY STRUCTURES

Ichthyosis Occasionally, the skin becomes very much overkeratinized so that it tends to crack and form coarse scales. Only very rarely is the condition as extreme as the cases illustrated in Fig. 140. Milder cases in which scales are smaller and thinner are more likely to be encountered.

Hypo- and Hypertrichosis Overabundance of hair in areas where the hair is normally sparse, or greater than normal length and thickness of the hair, is termed hypertrichosis. Cases showing a mild tendency in this direction are relatively common, but extreme cases are rare enough to have sideshow value ("JoJo, the dog-faced boy", "the bearded lady," etc.). The converse condition of hypotrichosis is occasionally seen. Very rarely the absence of hair is complete (atrachia), and in such cases there are usually defective nails and teeth.

Abnormalities of Pigmentation The melanin pigment which imparts the depth of tone to the skin is subject to a number of variations. It may be almost wholly wanting (albinism) or it may be overabundant (melanism). It may be spottily distributed (freckles) or the areas of irregularity may be much larger ("liver spots"). Very dense accumulations of melanin may be packed

gynecomastia, is undoubtedly the result of an underlying disturbance of the sex hormones, and may be associated with hermaphroditism although this is by no means necessarily the case. In the extraordinary case reported by Haenel (1928), which is one of the few on record of actual milk production from the mammary glands of an adult male, the man in question was the father of three children.

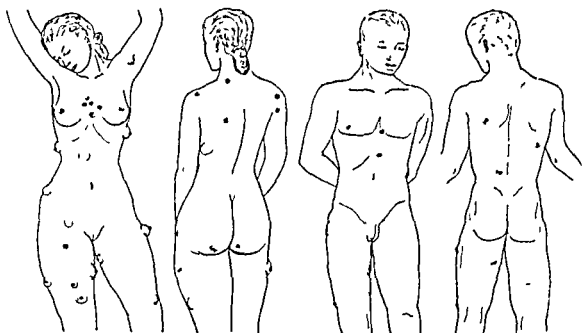


FIG 141 Schematic diagrams showing, collected on single subjects, all the unusual locations in which supernumerary nipples have been reported in the literature. Note that, although fewer cases are on record for males, the supernumerary nipples may occur in just as bizarre locations as in the female. Naturally the male rarely shows well-developed mammary gland tissue in connection with the aberrant nipples (Assembled and schematized primarily from the works of Surmont, and of Cholnoky.) The usual locations for supernumerary nipples are along the course of the "milk ridge" as indicated in Fig. 136.

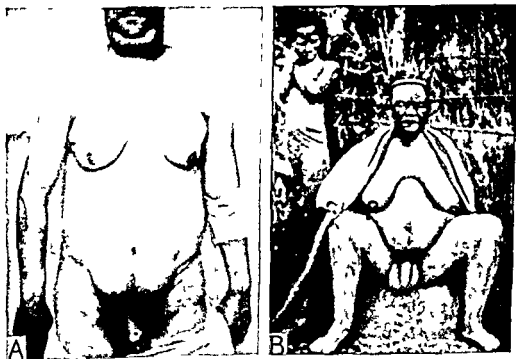


FIG 142 Two cases of gynecomasty (A, After Sailer B, After Schufeldt.)

gether as their peri- and epimysial sheaths. With a still more liberal elastic component, a similar connective tissue holds nerves and blood vessels in their mobile relations to muscle groups, or supports the clusters of fat cells that lie in the subcutaneous zones over the muscles.

The specialized characteristics of a connective tissue, such as its particular mixture of collagenous and elastic fibers, are established relatively late, and their development can be considered more profitably in a course in histology than in the present connection. It is, nevertheless, pertinent for us at this time

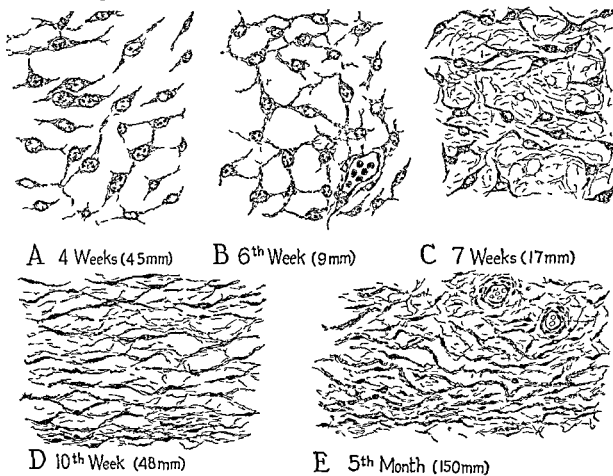


FIG. 143 Five stages in histogenesis of loose fibro-elastic connective tissue. All drawings, by projection, at a magnification of 500.

to see the general steps by which all such connective tissues take shape. In embryos toward the close of the first month of development, mesenchymal cells are rapidly coming to occupy most of the free space between the deeper lying structures and the superficial ectoderm. The cells at this stage, however, still tend to remain fairly independent of one another (Fig. 143, A). By the sixth week, the processes of adjacent cells begin to unite so that a syncytial network is formed (Fig. 143, B). At the same time, delicate fibrils commence to make their appearance along the peripheral areas of the cytoplasm. Toward the end of the second month, the fibrils are quite abundant and, probably because the cells are continually shifting their position more or less through their ameboid activity, some of the fibers begin to be left clear of the cytoplasm of the cells which formed them and to appear free in the intercellular

Connective Tissues and Skeletal System

The adult tissues grouped together by the histologist as the connective and supporting tissues differ widely among themselves as to structural details and mechanical properties. But in spite of their variety these tissues are all similar in that the secreted parts, rather than the cells themselves, carry out the functional rôle characteristic of the tissues. It is the secreted, fibrous portion of the binding connective tissues which ties together various other tissues and organs, it is the secreted matrix of cartilage and of bone which affords rigid support and protection to soft parts and furnishes a lever system on which the muscles may be brought into play.

The cellular elements of these tissues must not be overlooked, however, in emphasizing the functional importance of the cell products. The cells are, so to speak, the power behind, in that they extract the appropriate raw materials from the circulation, elaborate them within their cytoplasm, and deposit the characteristic secretion as an end-product. Moreover, after the fiber is formed or the matrix is laid down, it is dependent on the cells for its maintenance in a healthy active condition.

Embryologically, the entire connective-tissue group arises from mesenchymal cells. It is not surprising, in view of their closely related functions and their derivation from a common type of ancestral cell, that one type of connective tissue may be converted into or replaced by another. This facility for changing the type of specialization, or plasticity as it is called, is a thing we shall have occasion to emphasize in various connections in the discussion of the connecting and supporting tissues.

HISTOGENESIS OF FIBROUS CONNECTIVE TISSUES AND CARTILAGE

Fibro-elastic Connective Tissue In the adult we recognize various types of connective tissues according to the kind and arrangement of the fibers present. The most abundant and widespread of the connective tissues is the so-called fibro-elastic type. This tissue is composed of an interlacing system of tough bundles of collagenous fibers and elastic fibers which give to the system resilience and adaptability to positional changes. It is this type of tissue which, with the emphasis on its collagenous fiber component, forms the connective-tissue investment of a bone known as its periosteum, or the covering layer of cartilage called perichondrium. With a more generous admixture of elastic fibers this same general type of connective tissue holds muscle elements to-

dorsal accumulations of it have been called the "hibernation glands" Its significance is not well understood

Cartilage Formation The first indication of the impending formation of cartilage is the aggregation of an exceedingly dense mass of mesenchymal cells This cell mass gradually takes on the shape of the particular cartilage to be formed The histogenetic changes involved are not at first conspicuous During the period of preliminary massing the cells have been migrating in from surrounding regions and also increasing the local congestion by their own rapid proliferation As they are packed in together they lose their processes and become rounded (Fig 144, A) When it seems as if no more cells could possibly be crowded in, the course of events changes and the cells begin to separate from one another This is due to the fact that they are becoming active in secreting, and the accumulation of their secretion is gradually forcing them farther and farther apart till they come to be isolated from one another in the matrix they have produced (Fig 144, B, C) Such a method of increase in mass, where there are many scattered growth centers contributing independently to the increase in bulk of the whole, is known as *interstitial growth* This interstitial growth of young cartilage stands in sharp contrast to the *appositional growth* of such rigid substances as bone, or dentine, or enamel, where the matrix is laid down in successive layers one upon another Obviously interstitial growth implies plasticity of the substance produced Were the substance produced unyielding, the very activity of a number of growth centers within it would soon crowd these centers to obliteration

As the cartilage matrix is increased in amount the cartilage cells embedded in it become more widely separated from each other (Fig 144, D) At the same time the matrix becomes more rigid with a resultant checking of interstitial growth The cells continue to secrete to a certain extent, however, as evidenced by the fact that in mature cartilage the matrix immediately surrounding the cells becomes more dense than the rest of the matrix This area of denser matrix around the lacuna in which the cell lies is known as the capsule As the cartilage grows older the capsules become more conspicuous and many of them come to contain more than one cell These nests of cells in a common capsule are the result of cell divisions, following which the daughter cells are held imprisoned in the original capsule of the mother cell—further evidence of the loss of plasticity in the matrix These latter changes involving capsule formation occur for the most part postnatally and are not covered in Fig 144, which was drawn to show the appearance of embryonic cartilage

The formation of a matrix so rigid that interstitial growth is checked takes place first centrally in an area of developing cartilage When the center has become too rigid for interstitial growth to continue, appositional growth begins to take place peripherally While the cartilage has been increasing in mass it has been acquiring a peripheral investment of compacted mesenchyme This investing layer of mesenchyme soon becomes specialized into a connective-tissue covering called the perichondrium (Fig 144) The layer of the perichondrium next to the cartilage is less fibrous and more richly cellular

spaces (Fig 143, C) When fibers begin to become a conspicuous part of the young connective tissue, the term fibroblast is very likely to be used in referring to the cells of mesenchymal origin which are producing the fibers

After these early stages, the young connective tissue soon takes on a quite characteristic appearance One begins to see a definite pattern in the direction of the fibers, correlated with the mechanical conditions under which the tissue is commencing to function (Fig 143, D) By the fifth month, the fibers begin to run in definite bundles (Fig 143, E) and there is apparently a chemical change by which the primitive embryonic fibers are converted into true white (collagenous) fiber bundles Elastic fibers do not make their appearance as early as do the collagenous, and special stains are necessary to demonstrate them Only after they have become large and well differentiated are they recognizable in the ordinary hematoxylin and eosin preparations It seems probable that the elastic fibers are secreted by connective-tissue cells (fibroblasts) in the same general manner as the white (collagenous) fibers Their chemical composition and physical properties are quite different, however, and they tend to run singly rather than in bundles as do the white fibers

Adipose Tissue Scattered at various locations in the developing connective tissues can be found mesenchymal cells which have the ability to store lipoidal materials These are the forerunners of the fat cells of adult histology Recent studies seem to indicate that these cells differentiate specifically at a relatively early period It seems doubtful if a mesenchymal cell which has once become a fibroblast can later become transformed into a fat cell, and probably any new adipose-tissue cells that are added in the adult come from a reserve of undifferentiated mesenchymal cells It is ordinarily during the fourth month that the first indications of fat storage can be demonstrated in the fetus by specific staining for lipoidal materials At first the fat accumulates in the form of many small droplets within the cytoplasmic area of the cells These droplets later tend to increase in size and coalesce, causing the cell to round out and enlarge, and crowding the nucleus toward the periphery While fat storage can ordinarily be demonstrated histologically by the fourth month, extensive accumulations of subcutaneous fat usually do not begin to be laid down until the last two months of embryonic life The paradoxically old and wizened appearance of a premature infant is due in large measure to the fact it lacks the fat accumulation ordinarily acquired in the last month of pregnancy

There are at various locations in the fetus, especially along the coelomic side of the dorsal body-wall, groups of fat cells that tend to retain their multiple small lipid droplets long after such droplets have coalesced in other fat cells in the body In man these peculiar cells can still be recognized at birth but during infancy they become indistinguishable from the ordinary fat cells In the cat, according to Sheldon, these polyvacuolate fat cells persist until maturity In some of the rodents this type of adipose tissue persists throughout life In these forms this peculiar type of fat has a brownish color and the main

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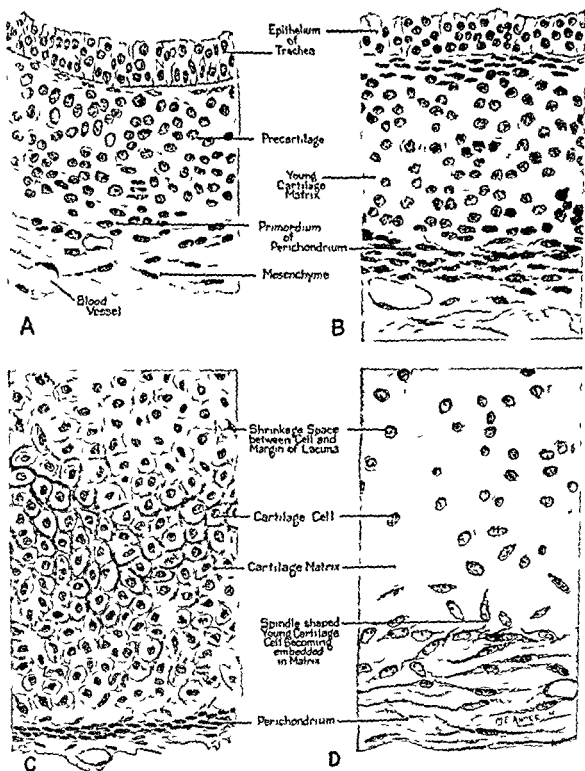


FIG 144 Stages in histogenesis of cartilage (Camera lucida drawings, $\times 500$) A, Tracheal cartilage from embryo of eighth week (C-R, 23 mm) B, Tracheal cartilage from embryo of ninth week (C-R, 33 mm) C, Cricoid cartilage from embryo of tenth week (C-R, 48 mm) D, Tracheal cartilage from fetus of twenty-fifth week (C-R, 240 mm)

than the outer layer, and the cells in it continue to proliferate rapidly and become active in the secretion of cartilage matrix. For this reason it is known as the chondrogenetic layer of the perichondrium. In actively growing cartilage it is possible to see spindle-shaped cells which recently were a constituent of the perichondrium being incorporated into the cartilage matrix (Fig 144, D). It is through the activity of the chondrogenetic layer that the cartilage continues to grow peripherally, by apposition, long after interstitial growth has ceased in the matrix first formed.

HISTOGENESIS OF BONE

Bone does not form in vacant spaces in the growing body. It is always laid down in an area previously occupied by some less highly specialized member of the connective-tissue family. This replacement of one tissue by another, in the formation of bone, well exemplifies the developmental plasticity of the connective and supporting tissues which was commented on at the beginning of this chapter. The formation of some bones begins in areas already occupied by connective tissue. Such bones are said to be intramembranous in origin, or are spoken of as "membrane bones." Other bones are laid down in areas already occupied by cartilage. In this case they are said to be endochondral in origin, or are called "cartilage bones." *It should be clearly borne in mind that these terms apply solely to the method by which a bone starts to develop and do not imply any differences in histologic structure, once the bone is fully formed.*

Likewise we should know at the outset what histologists mean when they speak of cancellous bone and compact bone. These terms refer not to the method of origin of the bone but to its density when fully formed. Developmentally, all bone goes through the spongy or cancellous stage. Some bones stay for the most part in such a condition throughout life. Others, by further deposition of bone matrix, become compact. Most bones when fully formed are compact in some areas and cancellous in others, and when a bone as a whole is referred to as being cancellous or compact, it is merely a loose designation on the basis of the predominant condition.

The subject of bone development can be presented most simply if we take up first the formation of primary cancellous bone intramembranously, then the method by which this same type of spongy bone is formed within cartilage, and finally the changes by which cancellous bone, formed in either of the above ways, may become secondarily compact.

INTRAMEMBRANOUS BONE FORMATION

Early Preparatory Changes in Mesenchymal Areas In an area where intramembranous bone formation is about to begin we find an abundance of mesenchymal cells congregated and numerous small blood vessels present. Here and there throughout the area the mesenchymal cells exhibit a tendency to cluster together in strung-out groups running in various directions. If we study a group of this type which has been aggregated for a short time we can make out the beginning of a definite plan of organization. Constituting a sort

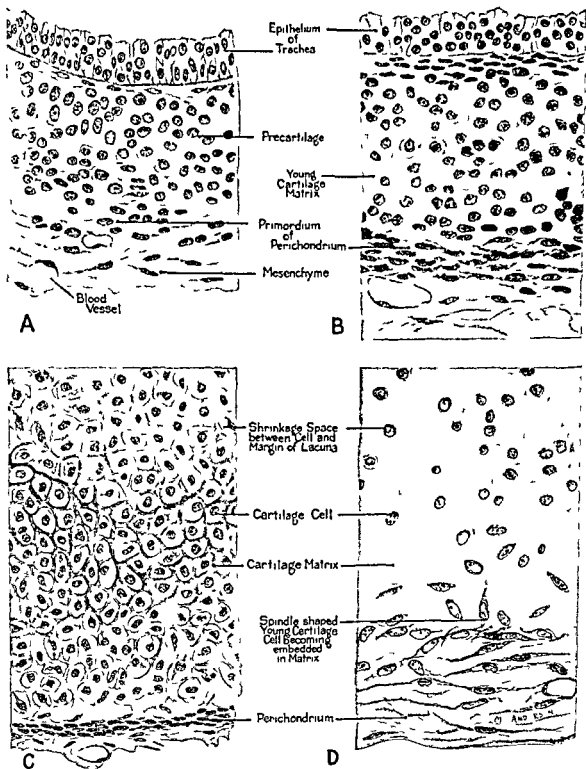


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concrete gives form and hardness. So in bone the osseous framework imparts cohesive strength and resilience, while the calcium salts with which the framework is impregnated give to the completed matrix form and rigidity.

Deposition of Calcium Salts Immediately after the osseous framework has been laid down, the deposition of calcium salts begins. In fact, one usually finds the calcium deposition beginning on the older part of a strand while its younger end is still being extended by the aggregation of more mesenchymal cells (Fig 145, A). Comparing the appearance of the cells ranged against the strand at its older end with those sprawling about its younger end, one sees that the cells at the older end have rounded out by retracting the processes so characteristic of undifferentiated mesenchymal cells. This change in shape is accompanied by deeper staining of the cytoplasm. Both these changes presage the beginning of the deposition of calcium compounds through the activity of these cells, and when they have reached this stage of specialization they are appropriately called osteoblasts. We should not, however, lose sight of the fact that they are cells from the same mesenchymal stock which formed the fibrous axis. They have merely been given a new name in deference to their further specialization and altered internal chemistry.

If we look at a strand on which the osteoblasts have been active for a time (Fig 145, B) we can readily see evidences of the two steps in the deposition of bone matrix. Next to the osteoblasts is a zone of osseous framework which takes very little stain. This is the newly deposited organic portion of the matrix as yet unimpregnated with calcium salts. It consists, as we have seen, of a feltwork of minute fibers so delicate and so closely matted together that it is very difficult in ordinary preparations to see the individual fibers at all. Slightly farther from the osteoblasts the matrix is densely stained (Fig 145, B). This part of the matrix has been impregnated with calcium salts, chiefly phosphates and carbonates, and has thereby been converted into true bone matrix. Even after most of the calcium salts have been removed from the osseous framework by treatment of the tissue with acids (decalcification) to permit the making of sections, the staining reaction is still apparent. This indicates that the osseous framework in which calcium has once been deposited is more or less permanently changed chemically even though the calcium is subsequently removed as completely as possible.

The calcium utilized by the osteoblasts is brought to them by the blood stream where it is apparently carried in soluble form, probably in organic linkage. It is interesting to note in this connection that the presence of calcium and of phosphates in the blood is not in itself all that is necessary for this process. There must be present also vitamins which in some way facilitate the extraction by the osteoblasts of these raw materials from the blood, and their deposition in insoluble form as part of the bone matrix. The absence from the system of vitamin D, especially, results in the formation of bone matrix deficient in calcium salts, a condition known medically as "rickets."

Lamellae and Trabeculae When ossification has progressed to such a point that the original strand is completely invested by bone matrix, we say a

of axis of the elongated group of cells there is a strand of delicate fibers which has been produced by the secretory activity of the cells. As this axial fibrous strand becomes more definite, the cells tend to become ranged more or less regularly about it so that when it is cut longitudinally a row of cells appears flanking it on either side (Fig. 145, A)

The Osseous Framework If one follows the axial fibrous strand from its frayed-out-looking younger end toward its thicker, older end, increasing difficulty is experienced in distinguishing the individual fibers. It is probable

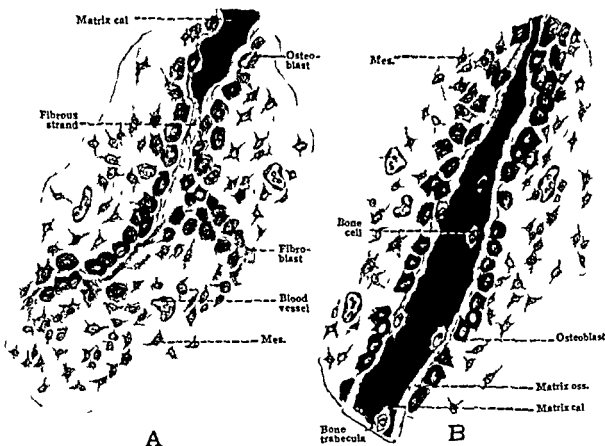


FIG. 145 Formation of trabeculae of membrane bone. Projection drawings from mandible of a pig embryo 130 mm. in length

Abbreviations matrix cal—osseous matrix impregnated with calcium salts, matrix oss—osseous matrix not yet impregnated with calcium salts, mes—mesenchymal cell

that this change in appearance is due to the saturation and matting together of the original collagenous fibers with osseomucoid, a substance closely akin chemically to collagen. The fibrous material thus formed constitutes a sort of preliminary framework in which calcium salts are subsequently deposited. This framework before it has been calcified is known by histologists as ossein or osteoid. The term bone matrix is properly applicable only to the ossein which has been impregnated with calcium salts. We may liken the matrix of bone to reinforced concrete. In the making of a road or a wall, a meshwork of steel is first placed in the forms and concrete is then poured in. The steel gives the finished structure tensile strength and a certain amount of elasticity. The

in contact with each other and fuse. Thus trabeculae, at first isolated, soon come to constitute a continuous system (Fig 147). Because of its resemblance to a latticework (Latin, cancellus), bone in this condition, where the tra-

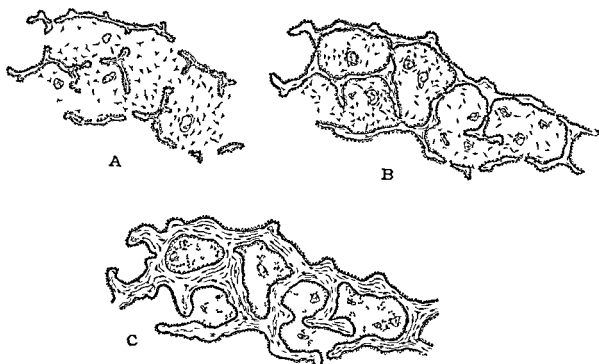


FIG 147 Diagrams showing stages in establishing of a characteristic area of primary cancellous bone by extension and coalescence of originally separate trabeculae

beculae are slender and the spaces between them extensive, is known as primary cancellous bone. The spaces between the trabeculae are known as marrow spaces.

ENDOCHONDRAL BONE FORMATION

As the term implies, endochondral bone formation goes on within cartilage. It can not be stated too strongly that cartilage does not, in this process, become converted into bone. Cartilage is destroyed and bone is formed where the cartilage used to be. The actual bone formation is essentially the same as in the case of membrane bone. The phenomena of special interest in connection with this type of bone development are those involved in the destruction of the cartilage preliminary to the formation of bone.

Cartilage Erosion When a mass of cartilage is about to be replaced by bone, very striking changes in its structure take place. The cells which have hitherto been secreting cartilage matrix begin to destroy the matrix. The lacunae become enlarged and a curious arrangement of the cartilage cells becomes evident. The cells erode the cartilage in such a manner that they become lined up in rows (Fig 148). This process of destruction continues until the cartilage is extensively honeycombed. Meanwhile the tissue of the perichondrium overlying the area of cartilage erosion becomes exceedingly active.

trabecula (little beam) has been formed (Fig 145, B). As the osteoblasts continue to secrete and thereby thicken the trabecula the new matrix added is not laid down uniformly. It is possible to make out in it markings which are suggestive of the growth rings of a tree. Apparently the osteoblasts work more or less in cycles, depositing a succession of thin layers of matrix. Each of these layers of the matrix is called a lamella (Fig 146). As the row of osteoblasts is forced back with the deposit of each succeeding lamella, not all the cells free themselves from their secretion. Here and there a cell is left behind and, as its former fellows continue to pile up new matrix, becomes completely buried

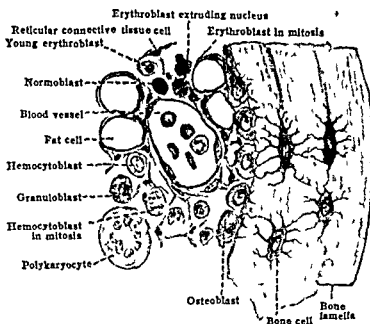


FIG 146 A small area of bone and adjacent marrow as seen in highly magnified decalcified sections

An osteoblast so caught and buried is called a bone cell (Fig 145, B), and the space in the matrix which it occupies is called a lacuna. The bone cells, thus entrapped, of necessity cease to be active bone formers, but they play a vital part in the maintenance of the bone already formed. They have delicate cytoplasmic processes radiating into the surrounding matrix through minute canaliculi. The processes of one cell come into communication with the processes of its neighbors (Fig 146). Thus the bone cells nearer to blood vessels absorb and hand on materials to their more remote fellows which in turn utilize these materials in maintaining a healthy condition in the organic part of the bone matrix. In all probability it is the senescence of the bone cells with the consequent lowering of their efficiency and the resultant deterioration of the osseous component of the matrix which is responsible for the decreased resiliency of the bones in advanced age.

Coalescence of Trabeculae to Form Primary Cancellous Bone As the various trabeculae in an area of developing bone grow, they inevitably come

There is rapid cell proliferation and the new cells, carrying blood vessels with them, begin to invade the honeycombed cartilage (Fig 148)

Deposition of Endochondral Bone It is a striking fact that during its formation cartilage is devoid of blood vessels, the nearest vessels to it being those in the perichondrium. The invasion of cartilage by blood vessels definitely announces its impending disintegration as cartilage, and at the same time is the initial step in the formation of bone. For this reason the enveloping layer of connective tissue, called, up to this time, perichondrium because of its relation to the cartilage, is now called periosteum because of the relations it will directly acquire to the bone about to be formed. *This change will not be confusing if we stop to think that both these terms are merely ones of relation, which translated mean, respectively, that tissue which surrounds cartilage, and that tissue which surrounds bone.* The important fact to bear in mind is that this enveloping layer of connective tissue is of mesenchymal origin and, therefore, contains cells of the stock that may develop into any of the connective-tissue family to which bone as well as cartilage belongs. Thus, when a mass of periosteal tissue (periosteal bud, Fig 148) grows into an area of honeycombed cartilage, it carries in potential bone-forming cells. These cells come to lie along the strandlike remnants of cartilage just as in membrane bone formation osteoblasts ranged themselves along fibrous strands. The actual deposition of bone proceeds in the same manner endochondrally as intramembranously, the only difference being that strandlike remnants of cartilage serve as axes for the trabeculae in one case, whereas in the other the deposit began on fibrous strands. Extensions and fusions of the growing trabeculae soon result in the establishment of typical cancellous bone similar to that formed intramembranously.

FORMATION OF COMPACT BONE FROM PRIMARY CANCELLOUS BONE

The difference between cancellous bone and compact bone is architectural rather than histological. The fundamental composition of the bone matrix, its lamellation, and the relations of the bone cells to the matrix, are the same in both cases. It is the way in which the bone matrix is arranged that distinguishes these two types of bone from each other. Cancellous bone is made up of a latticework of slender trabeculae enclosing large numbers of marrow spaces (Fig 147, C). In compact bone there has been a secondary deposit of lamellae in the marrow spaces, thus greatly increasing the density of the bone as a whole (Fig 149, d).

The essential differences between the two, and the way in which cancellous bone may become converted into compact bone, can be illustrated by a simple schematic diagram in which the lamellae are indicated by lines, thus emphasizing what we might call the lamellar architecture of the bone. Fig 149, 1 shows the arrangement of lamellae and marrow spaces in primary cancellous bone. The osteoblasts which have formed the trabeculae still lie along them

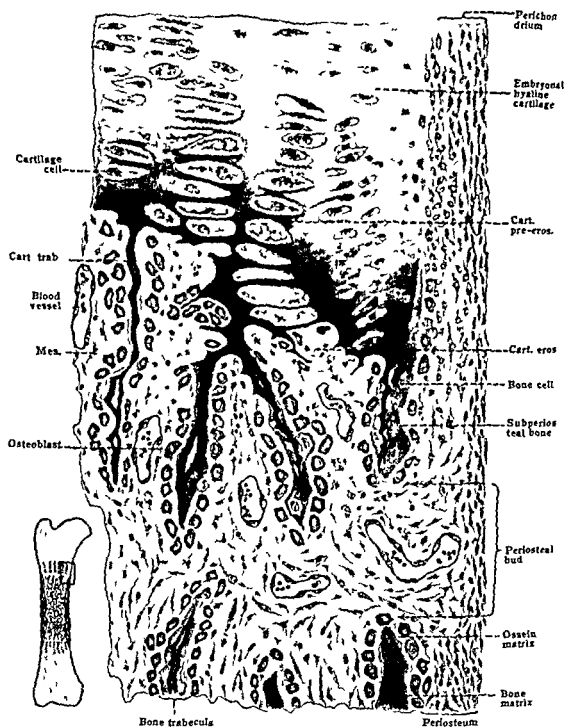


FIG 148 Drawing showing periosteal bud and an area of endochondral bone formation from the radius of a 125-mm sheep embryo Small sketch indicates location of area represented

Abbreviations Cart eros—area from which cartilage has recently been eroded, Cart pre eros—area with cartilage cells enlarged and arranged in rows presaging erosion, Cart trab—remnant of cartilage matrix which has become calcified and serves as an axis or core about which bone lamellae are deposited to form a bone trabecula, Mes—mesenchymal cell

anything like completeness. It should not be difficult, however, to become acquainted with the outstanding features in the formation of characteristic types of bones, as for example the sequence of events in the formation of a flat bone, the steps involved in the establishment and growth of a long bone, the way separate ossification centers appear in a common primordial cartilage mass and give rise to the various parts of such a bone as a vertebra, or to a composite cranial bone like the occipital. If one supplements such basic information on the different kinds of bones with a study of the manner in which joints are formed, one should have a reasonable working knowledge of the factors operative in the development of the skeleton as a whole. Such a background should be sufficient to permit ready and intelligent following up of the developmental details involved in the growth of any specific bones in which one may become interested.

Development of Flat Bones The flat bones, such as the bones of the cranium and face, are for the most part of intramembranous origin. We are, therefore, already familiar with the early steps in their development from our study of the histogenesis of membrane bone (Figs 145, 147). After a mass of primary cancellous bone has been laid down in a configuration which suggests that of the adult bone being formed, there appears about this mass a peripheral concentration of mesenchyme (Fig 150, A). This periosteal concentration of mesenchymal tissue contains cells which are potentially bone-forming, and which soon become active and deposit a dense layer of parallel lamellae about the cancellous center of the growing bone (Fig 150, B). Anatomically, this dense peripheral portion is known as the "outer table" of the bone. The inner portion, which in the flat bones usually remains cancellous, is called the diploe. The original mesenchymal tissue which remains in the marrow spaces of the diploe develops into characteristic "red bone marrow" rich in blood-forming elements (Fig 146).

The story of the growth of the mandible, a membrane bone which starts after the manner of flat bones but which later takes on a very elaborate shape and finally becomes largely compact, can be gleaned by a comparative study of Figs 172-174, 258, 261, and 263.

Development of Long Bones The long bones are characteristically of endochondral origin. The cartilage in which they are preformed is a temporary miniature of the adult bone. Ordinarily there are several ossification centers involved in the formation of long bones. The first one to appear is that in the shaft or diaphysis. The location of this center is shown schematically in Fig 151, A. Such details as the cartilage erosion which preceded its appearance and the manner in which the deposit of bone was initiated have already been considered (Fig 148). Our interest now is in the relation of such an endochondral ossification center to other centers, and to the formation of the bone as a whole.

Almost coincidently with the beginning of bone formation within the cartilage the overlying periosteum begins to add bone externally (Fig 151, B). In view of the fact that the bone-forming tissue carried into the eroded carti-

on the surface toward the marrow space—against the last lamella that was laid down. If the bone is to become compact, these osteoblasts enter on a period of renewed activity and deposit a series of concentric lamellae which progressively encroach on the marrow spaces. Frequently, if the marrow spaces are irregular, there is a preliminary rounding out of them by local resorption of the bone already formed (Fig 149, 2). This is then followed by the deposition of the concentrically arranged lamellae, sometimes called *Haversian lamellae* after the man who first described them in detail (Fig 149, 3). Because of their position with reference to the Haversian lamellar systems, the lamellae of the original trabeculae of the primary cancellous bone are usually called its *interstitial lamellae* when a bone has become compact.

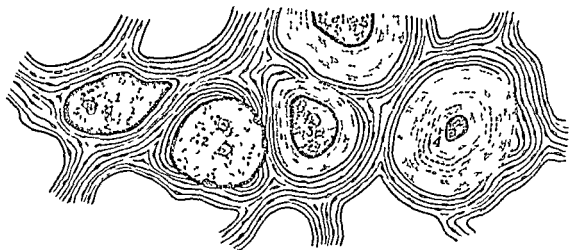


FIG. 149 Diagram showing transformation of cancellous to compact bone. The solid lines indicate the lamellae of primary cancellous bone, the dotted lines show the subsequently added concentric (Haversian) lamellae which nearly obliterate the marrow spaces of cancellous bone. The sequence of events is indicated by the numbers. Note that irregularly shaped spaces in the cancellous bone may be rounded out by absorption before the concentric lamellae are laid down.

By the formation of the new concentric lamellar systems the original marrow spaces are reduced to small canals (Haversian canals) into which have been crowded the blood vessels which formerly lay in the marrow spaces (Fig 149, 4). These canals maintain intercommunication with each other in the substance of the bone and constitute a network of pathways over which the bone receives its vascular supply. As compared with the marrow spaces of cancellous bone, however, they are very small and the gross appearance of a bone which has undergone this secondary deposit of concentric lamellae amply justifies characterizing it as "compact."

DEVELOPMENT OF THE SKELETON

Having become familiar with the ways in which the connective and supporting tissues are formed, we are ready to turn our attention to the manner in which they are built into the skeleton. We must recognize at the outset that the subject of skeletal development is far too extensive to be covered here with

increase in length This was long ago demonstrated experimentally by exposing a developing bone and driving into it three small silver pegs, two in the shaft and one in the epiphysis The distance between the pegs being recorded, the incision was closed and development allowed to proceed until a marked increase had occurred in the length of the bone On again exposing the pegs, the two in the shaft were found to be exactly the same distance apart as when they were driven in, but the distance between the pins in the shaft and that in the epiphysis had increased in proportion to the increase in the length of the bone This indicates clearly that the epiphyseal plates constitute a sort of temporary, plastic union between the parts of the growing bone Continued

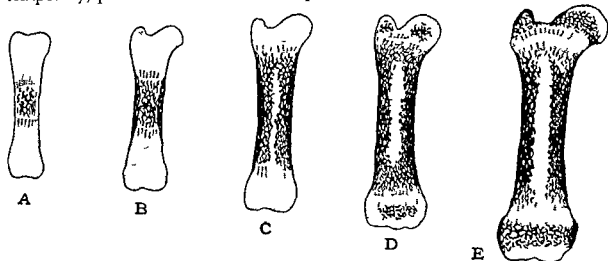


FIG 151 Diagrams showing progress of ossification in a long bone Stippled areas represent cartilage, black areas indicate bone A, Primary ossification center in shaft B, Primary center plus shell of subperiosteal bone C, Entire shaft ossified D, Ossification centers have appeared in the epiphyses E, Entire bone ossified except for the epiphyseal cartilage plates and articular surfaces

increase in the length of the shaft is accomplished by the addition of new bone at the cartilage plate These epiphyseal plates persist during the entire post-natal growth period Only when the skeleton has acquired its adult size do they finally become resorbed and replaced by bone which joins the epiphyses permanently to the diaphysis (Fig 177)

As the bone increases in length there is a corresponding increase in its diameter The manner in which this takes place is also susceptible of experimental demonstration If madder leaves, or some of the alizarin compounds extracted from them, are fed to a growing animal, the bone formed during the time the feeding is continued is colored red If the madder is discontinued, bone of normal color is again formed, but the color still remains in the bone laid down while madder was being added to the diet Thus it is possible, by keeping a record of alternate periods of feeding and withholding madder, and comparing these records with the resulting zones of coloration in a bone, to obtain very accurate information on the progress of bone growth The growth as one would expect is primarily subperiosteal, but there are many interesting details involved in the remodeling of the bone already formed as new bone is added

lage arose from the periosteum, this activity of the periosteum itself is not surprising. Moreover, we have already encountered this same phenomenon of subperiosteal bone formation in the laying down of the outer table of flat bones.

The ossification which starts at about the middle of the shaft soon extends toward either end until the entire shaft is involved (Fig. 151, C) leaving the two ends (epiphyses) still cartilage. Toward the end of fetal life, ossification centers appear in the epiphyses. The numbers and locations of these epiphyseal

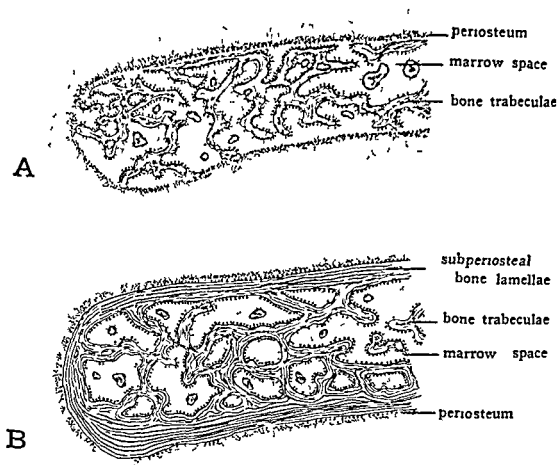


FIG. 150 Diagrams showing manner in which dense peripheral layer of a flat bone is formed by the deposition of subperiosteal lamellae about an area of primary cancellous bone.

centers vary in different long bones. In most cases there is at least one center in each epiphysis. Some of the phalanges are exceptions to this general rule, showing an epiphyseal center at only one end. In some of the larger long bones there are two centers in one epiphysis and one in the other. At its elaborately shaped proximal end the femur eventually shows three epiphyseal ossification centers, one in the head, one in the greater, and one in the lesser trochanter.

Between the bone formed in the diaphysis and that formed in the epiphysis there persists a mass of cartilage, known as the epiphyseal plate, which is of vital importance for the growth in length of the bone. We should expect from the rigidity of bone matrix that interstitial growth could not account for its

increase in length. This was long ago demonstrated experimentally by exposing a developing bone and driving into it three small silver pegs, two in the shaft and one in the epiphysis. The distance between the pegs being recorded, the incision was closed and development allowed to proceed until a marked increase had occurred in the length of the bone. On again exposing the pegs, the two in the shaft were found to be exactly the same distance apart as when they were driven in, but the distance between the pins in the shaft and that in the epiphysis had increased in proportion to the increase in the length of the bone. This indicates clearly that the epiphyseal plates constitute a sort of temporary, plastic union between the parts of the growing bone. Continued

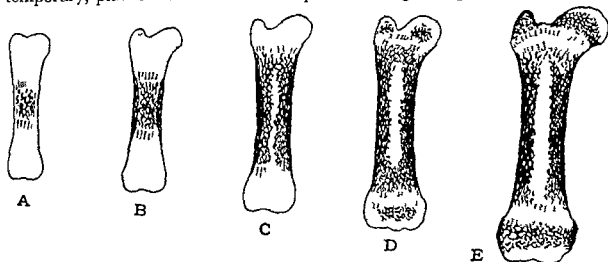


FIG 151 Diagrams showing progress of ossification in a long bone. Suppled areas represent cartilage, black areas indicate bone. A, Primary ossification center in shaft. B, Primary center plus shell of subperiosteal bone. C, Entire shaft ossified. D, Ossification centers have appeared in the epiphyses. E, Entire bone ossified except for the epiphyseal cartilage plates and articular surfaces.

increase in the length of the shaft is accomplished by the addition of new bone at the cartilage plate. These epiphyseal plates persist during the entire post-natal growth period. Only when the skeleton has acquired its adult size do they finally become resorbed and replaced by bone which joins the epiphyses permanently to the diaphysis (Fig. 177).

As the bone increases in length there is a corresponding increase in its diameter. The manner in which this takes place is also susceptible of experimental demonstration. If madder leaves, or some of the alizarin compounds extracted from them, are fed to a growing animal, the bone formed during the time the feeding is continued is colored red. If the madder is discontinued, bone of normal color is again formed, but the color still remains in the bone laid down while madder was being added to the diet. Thus it is possible, by keeping a record of alternate periods of feeding and withholding madder, and comparing these records with the resulting zones of coloration in a bone, to obtain very accurate information on the progress of bone growth. The growth as one would expect is primarily subperiosteal, but there are many interesting details involved in the remodeling of the bone already formed as new bone is added.

Very early in the growth of a long bone resorption begins to take place in the axial part of the shaft, resulting in the establishing of the marrow canal (Fig 151, C-E) This early assumption of tubular form is interesting from a mechanical standpoint for such a shape is well known to afford maximum strength with minimum weight The hollow shaft of the young bone is at first cancellous, but as its growth proceeds it soon becomes converted into compact bone by the secondary formation of concentric lamellar systems Around the outside of the bone which has thus newly become compact, additional lamellae are formed beneath the periosteum These lamellae laid down parallel to the surface are called outer circumferential lamellae (Fig 152, A) Even without the aid of madder feeding a very interesting record of the manner in which the further growth in diameter occurs in such a bone can be made out from thoughtful study of its lamellar architecture as seen in sections It is necessary only to recall the way in which lamellae are formed as thin layers of bone matrix laid down on whatever constituted the substratum at the moment of their deposition In young bone the substratum for each new lamella is ordinarily the unaltered contour of a recently formed lamella in the same system Under such circumstances the lamellar pattern is very regular (Figs 149, 152, A)

But as peripheral growth and central resorption occur in a round bone there must be readjustments in the Haversian systems as well as in the circumferential lamellae When it is recalled that the blood vessels nourishing a bone reach all parts of it by way of the Haversian canals, it becomes self-evident that the canals must change their relations within the bone in such a manner that the continued vessels do not have their blood flow interrupted This is brought about by periods of resorption in which the lamellae of an established Haversian system are excavated in the direction toward which growth is taking place When lamellae start to form again following such a period of eccentric resorption, there is the overriding of the old system by the new, the new lamellae (Fig 152, B, a_2) forming against the lamellae of the older system which have been cut across by resorption (Fig 152, B, a_1) Wherever new lamellae are laid thus against older ones after an interval of interrupted deposition, or after a phase of resorption, there are particularly evident lines of interlamellar demarcation constituting what have been called "cementing lines" (Fig 152, C) The formation of such cementing lines, and the manner in which the more recently formed lamellar systems cut across older systems which have evidently suffered partial resorption, writes an unmistakable record of the steps in bone growth

Development of Joints In an area where a freely movable joint (diarthrosis) is to be formed between two skeletal members, there is at first only a vaguely outlined precartilaginous concentration of mesenchyme (Note the conditions in the appendage buds, Fig 155) Gradually the mesenchyme becomes perceptibly more densely aggregated in areas where cartilage formation is about to start (Fig 163, A, C) As the cartilage miniatures of the future bones become better defined, the joint becomes localized as an area between them,

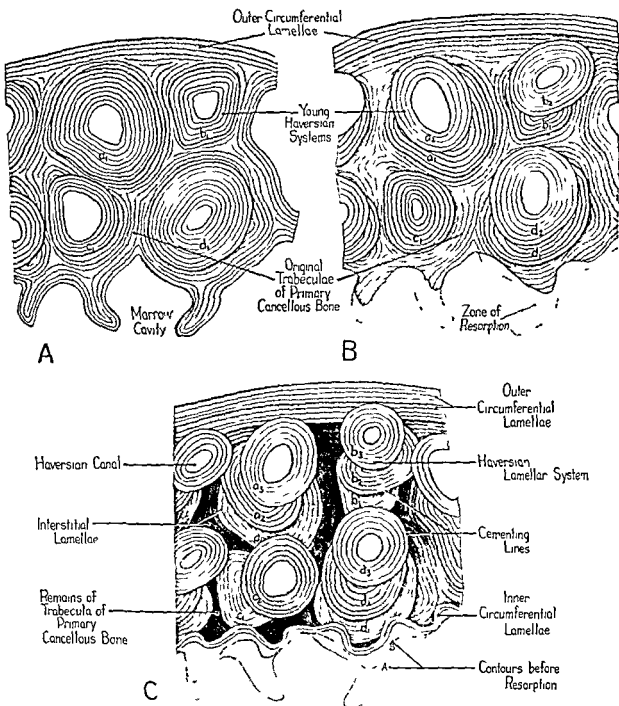


FIG 152 Schematic diagrams illustrating changes in Haversian systems of shaft of a long bone which are involved in its growth in diameter. Depth of shading indicates relative age of lamellae, oldest being represented as darkest. Certain of the lamellar systems have been identified by letters and numbers to facilitate following growth changes. Thus, for example, the succession of Haversian lamellar systems formed in relation to a particular Haversian canal have been designated as a_1 , a_2 , a_3 .

where the mesenchyme is less concentrated (Fig 153, A). When the perichondrium takes shape, it extends around the ends of the skeletal members so that where the joint is to be formed there is for a time an area of loosely woven young fibrous connective tissue (Fig 153, B).

Meanwhile, ossification starts in the shafts of the bones, but their epiphyseal ends remain cartilaginous. The thinning out (Fig 153, C) and final

disappearance (Fig 153, D) of the connective tissue from around the epiphyses establishes the joint cavity. Even after epiphysal ossification centers have appeared, the articulating ends of the bones at a diarthrodial joint continue to be capped by cartilage which provides a smooth bearing surface lubricated by the synovial fluid in the joint cavity.

The ligaments of the joint are formed by further development of the investing connective tissue which was retracted and concentrated peripherally to form the joint capsule. Eventually this young connective tissue of the ligamentous capsule becomes strengthened by the addition of more and more heavy, white (collagenous) fiber bundles. The ends of certain of these bundles become buried in the expanding tissues of the heads of the bones adjacent to the joint, thus holding the articulating members in proper relation to each other.

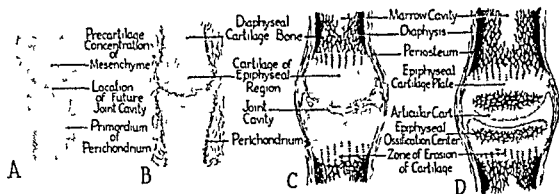


FIG 153 Schematic diagrams showing four stages in development of a joint

In the formation of a joint between two long bones, such as that covered in the foregoing generalized description, there is, from the first, cartilage at the joint surfaces. In the case of a diarthrodial joint formed between two membrane bones, such as the temporomandibular articulation, the sequence of events is somewhat different. Where the growing bones come to abut on each other at the site of their future articulation, there is a layer of connective tissue formed by the coalescence of the periosteal layers of the two bones. This young connective tissue forms a thin layer of cartilage over the articulating surfaces, and is then withdrawn to form a joint cavity in a manner similar to that described for the joints between long bones.

In the formation of joints in which little free movement is permitted (synarthroses) the striking difference in the course of events is the failure of the investing connective tissue to open up and produce a joint cavity. Instead it persists, holding the two bones more or less rigidly together. In different synarthrodial joints the intervening layer of young connective tissue differentiates in various ways. There may be a thin layer of white fibrous connective tissue holding the bones close together and practically immovable on each other, as is the case with the bones of the cranium. Such a line of union is called a *suture*. The uniting connective tissue may be in the form of cords or bands as, for example, the stylohyoid ligament (Fig 169), or the yellow elastic ligaments connecting the laminae of the vertebrae. Such a type of union in

which the bones are held together by connective tissue is spoken of as a *syn-desmosis*. Again, as is the case with the centra of the vertebrae, bones may be held together by intervening fibrocartilage. Such a union is a *synchondrosis*.

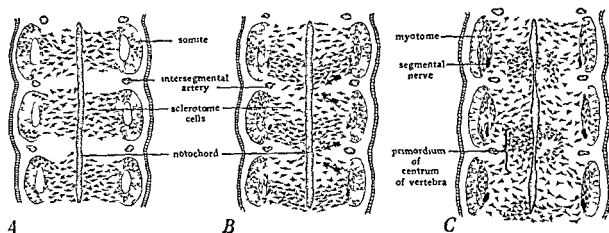


FIG 154 Semischematic coronal sections through dorsal region of young embryos to show how vertebrae became intermyotomal in position. Note that the primordium of a centrum is formed by cells originating from sclerotomes of both adjacent pairs of somites.

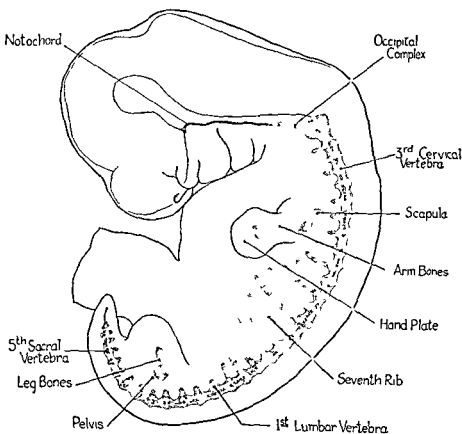


FIG 155 Diagram of precartilaginous primordia in a 9 mm human embryo (Adapted from several sources, chiefly the work of Bardeen)

When a synarthrosis originally formed by connective tissue (e.g., suture in the skull), or by cartilage (epiphyseal union in embryo or child), grows together by the replacement of such intervening tissues by bone we have a *synostosis*.

Formation of Vertebrae and Ribs The development of the vertebrae and the ribs is of particular interest both because they are so important in the skeleton as a whole, and because of the interesting manner in which they develop. Their growth well exemplifies the formation of separate ossification centers within a common primordial cartilage mass, and the subsequent coalescence of these centers to form an organized whole.

In studying young embryos we traced the history of the mesodermic somites through their early differentiation. It will be recalled that from the

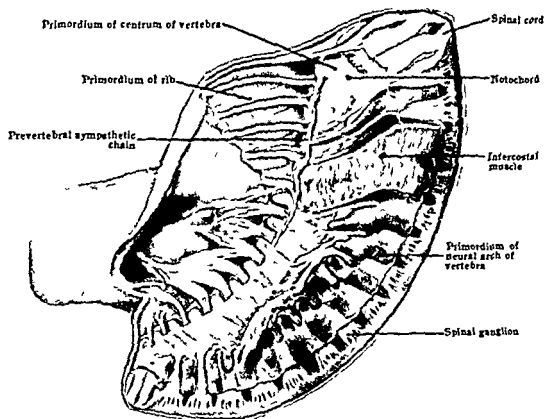


FIG. 156 Reconstruction showing configuration of precartilaginous concentrations of mesenchyme which are the primordia of the vertebral column and ribs (After Bardeen and Lewis, *Am J Anat*, Vol 1, 1901.) The reconstruction represents a dissection of the lower half of a human embryo of 9 mm. Compare with the schematic lateral view of Fig. 155.

ventromesial face of each somite there arises a group of mesenchymal cells called collectively a sclerotome (Fig. 63). These cells migrate from either side toward the mid-line and become aggregated about the notochord. From these masses of cells the elements of the vertebral column are destined to arise.

The first significant change which takes place in these primordial masses is the clustering of sclerotomal cells, derived in part from each of the two adjacent somites, into groups which are located opposite the intervals between the myotomes. In studying series of transverse sections this arrangement is easy to overlook unless the density of the cells about the notochord is carefully noted in passing from section to section. It shows very clearly, however, in frontal (coronal) sections (Fig. 154). Each of these cell clusters is the pri-

mordium of the centrum of a vertebra. Once formed they rapidly become more dense and more definitely circumscribed. Soon after the centrum takes shape, paired mesenchymal concentrations extending dorsally and laterally from the centrum establish the primordia of the neural arches and of the ribs (Figs 155, 156)

The stage in which the earliest parts of the skeleton to become recognizable are sketched in mesenchymal concentrations, is frequently spoken of as the blastemal stage (Fig 155). It is rapidly followed by the cartilage stage. In the development of the spinal column conversion to cartilage begins in the blastemal mass first in the region of the centrum and then chondrification

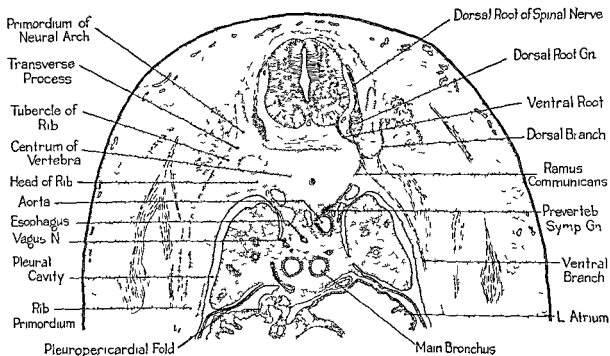


FIG 157 Transverse section of a 20-mm (early eighth week) human embryo to show the developing vertebra and ribs. The section slants somewhat so that the branches of the spinal nerve show especially well on the right (University of Michigan Coll., EH 253)

centers appear in each neural, and each costal process. These spread rapidly until all the centers fuse and the entire mass is involved. The cartilage miniature of the vertebra thus formed (Fig 157) is at first a single piece showing no lines of demarcation where the original centers of cartilage formation become confluent, and no foreshadowing of the separate parts of which it will be made up after the cartilage has been replaced by bone. By the time ossification begins, the rib cartilages become separated from the vertebra (Fig 158) but the vertebra itself remains in one piece.

The locations of the endochondral ossification centers which appear in a vertebral cartilage are indicated schematically in Fig 159, A. It is easy to see how the spreading of these centers of bone formation will establish the conditions which exist in the fully formed vertebra (Fig 159, B-E). The median ossification center gives rise to the centrum. The centers in the neural processes extend dorsally to form the laminae and complete the neural arch. The

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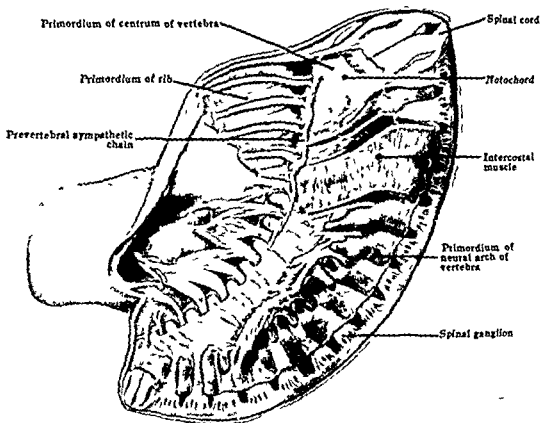


FIG. 156 Reconstruction showing configuration of precartilaginous concentrations of mesenchyme which are the primordia of the vertebral column and ribs (After Bardeen and Lewis, *Am J Anat*, Vol 1, 1901) The reconstruction represents a dissection of the lower half of a human embryo of 9 mm. Compare with the schematic lateral view of Fig. 155.

ventromesial face of each somite there arises a group of mesenchymal cells called collectively a sclerotome (Fig. 63). These cells migrate from either side toward the mid-line and become aggregated about the notochord. From these masses of cells the elements of the vertebral column are destined to arise.

The first significant change which takes place in these primordial masses is the clustering of sclerotomal cells, derived in part from each of the two adjacent somites, into groups which are located opposite the intervals between the myotomes. In studying series of transverse sections this arrangement is easy to overlook unless the density of the cells about the notochord is carefully noted in passing from section to section. It shows very clearly, however, in frontal (coronal) sections (Fig. 154). Each of these cell clusters is the pri-

In the light of the regular presence of a reduced costal component in the cervical vertebrae, it is not surprising that a well-developed cervical rib associated with the lowest cervical vertebra should be one of the less unusual

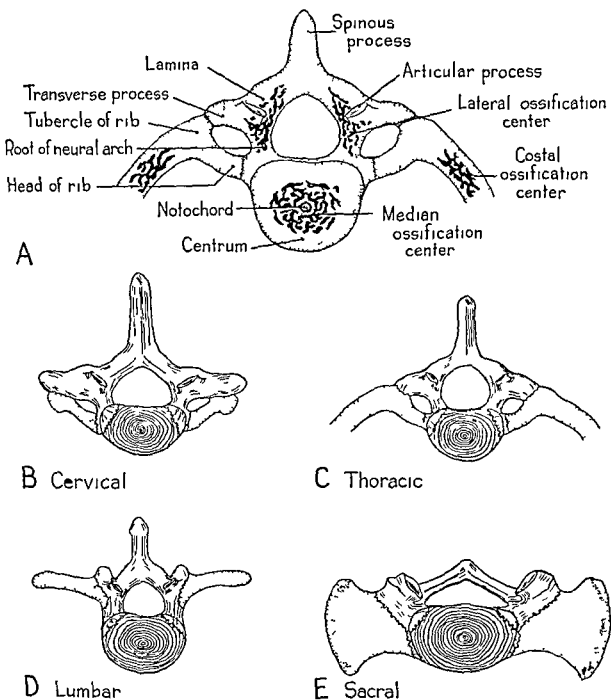


FIG 159 The component parts, and the locations of the ossification centers in developing vertebrae A, Diagram showing locations of various ossification centers in a thoracic vertebra and the associated ribs B-E, Drawings showing characteristic components of vertebrae from different levels Neural arch component is represented by line shading, costal component by stippling, and centrum by concentric markings

skeletal anomalies (Fig 161, A) In like manner a supernumerary rib may be formed in association with the first lumbar vertebra Less readily explicable on an embryological basis is the abnormal condition sometimes seen in which a rib forks as it joins the sternum (Fig 161, B)

spinous process is formed by a prolongation of these same centers beyond their point of meeting, dorsal to the neural canal. The transverse processes with which the tubercles of the ribs articulate are formed by the lateral extension of the centers appearing in the neural processes. Ventrally the neural process centers extend to and fuse with the centrum.

The shaft of the rib is formed by extension of its primary ossification center (Figs 159, 173, 174). After birth, secondary epiphyseal centers appear in the tubercle and in the head of the rib. During the growth period they remain

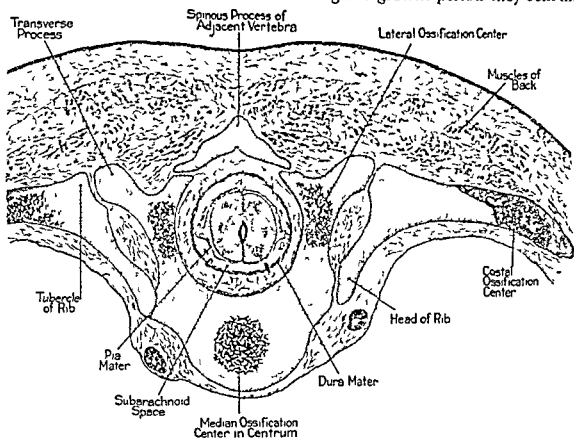


FIG 158 Transverse section from a human embryo of the twelfth week (C-R, 72 mm) to show the developing vertebra and ribs (University of Michigan Coll., EH 205, D, projection drawing, $\times 15$)

separated from the shaft by persistent cartilage plates in the manner described in discussing the development of long bones. Fusion of these secondary epiphyseal centers with the shaft of the rib does not take place until the skeleton has acquired its adult dimensions.

The foregoing discussion has been based on a thoracic vertebra in which the relations of the rib to the vertebra show most clearly. All the vertebrae have the costal element represented, although it is greatly reduced and modified in other regions than the thoracic. A study of Fig 159, B-D, in which the components of vertebrae from the cervical, thoracic, lumbar, and sacral regions are schematically indicated, will make the homologies apparent. With these homologies in mind, it is sufficiently evident, without going into further detail, how the vertebrae of all levels arise by a process essentially similar to that described for the thoracic vertebra.

Formation of Sternum It was pointed out in connection with the establishing of the heart that mid-ventral structures tended to appear first on either side of the mid-line and then converge toward it as development progressed. This is obviously correlated with the manner in which vertebrate embryos start to develop spread open mid-ventrally on top of the yolk-sac. It is not surprising, therefore, that the first suggestion of the sternum is in the form of a pair of bandlike concentrations of mesenchymal cells (Fig 162, A). As these bands become converted into precartilagel they converge toward the mid-line and start to fuse with each other, beginning cephalically (Fig 162, B). At the same time the rib cartilages have been extending from the vertebrae toward the sternum. By the ninth week the sternum is established in the mid-line and

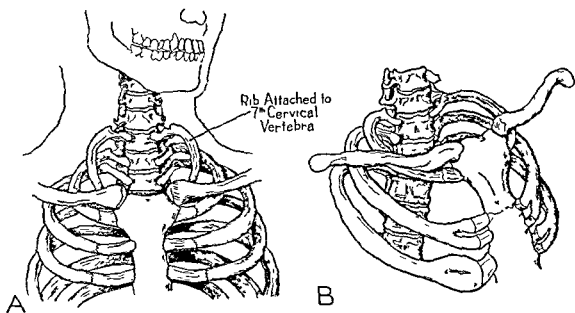


FIG 161 Abnormalities of the ribs A, Cervical ribs (Redrawn after Corning) B, Ribs with bifurcated sternal ends (Redrawn after Arey)

the ribs have grown to meet it (Fig 162, C). At this stage the sternum and the parts of the ribs attached to it have become cartilage, and ossification has already commenced in the parts of the ribs adjacent to the vertebrae (Fig 173).

Following its establishment in the mid-line, there are curious secondary transverse divisions of the sternum into a series of separate cartilages called sternbrae. This condition does not seem to play any significant rôle in the further development of the sternum, although there is some tendency for its multiple ossification centers to form in the centers of the sternbrae. Instead of all being single median centers as shown in Fig 162, D it is not uncommon for the centers in some of the sternbrae to be paired, right and left. The final coalescence of the ossification centers in the sternum does not take place until full maturity is attained (Fig 160).

The commonest anomalies of this region—cleft sternum, perforate sternum, and notched xiphoid process—are all obviously correlated with the paired arrangement of the sternal primordia.

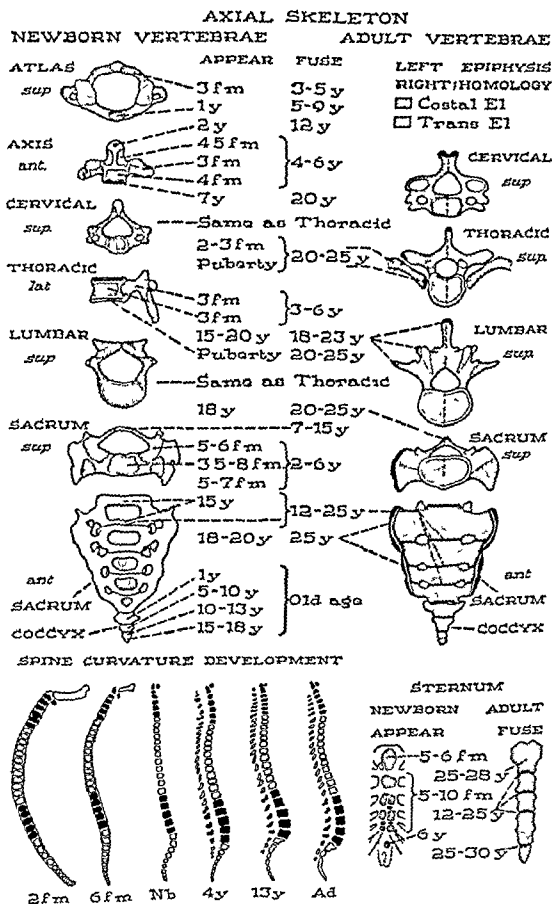
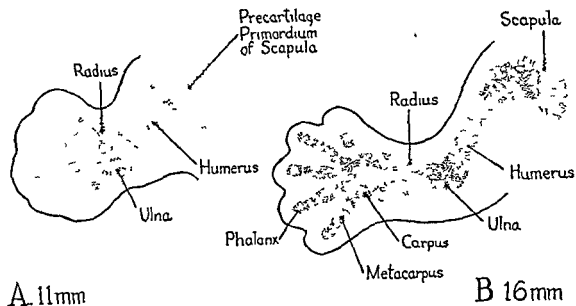
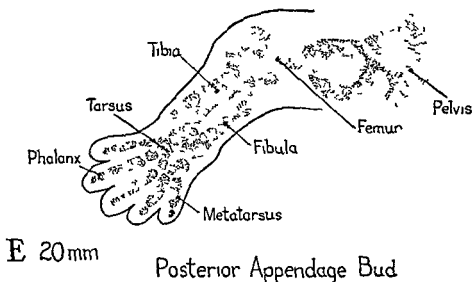
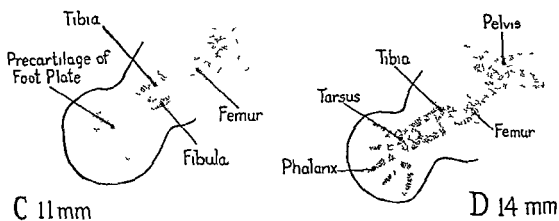


FIG 160 A schema of the development of the spinal column (From Scammon, in Morris "Human Anatomy," after J G Graca and C R Noback)



Anterior Appendage Bud



Posterior Appendage Bud

FIG 163 Early stages in development of the skeleton of the appendages (Modified from Bardeen and Lewis, *Am J Anat*, Vol 1, 1901) The fine stippling in the drawings of the younger stages indicates precartilag concentrations of mesenchyme, the more sharply circumscribed and coarser stippling of the older stages represents cartilage

Appendicular Skeleton Broadly speaking, the term appendicular skeleton may be taken to include the pectoral and pelvic girdles, as well as the bones of the appendages themselves. In their basic plan of structure the arm and leg are closely comparable. The different way in which they are rotated and bent during development somewhat masks some of their homologies, but

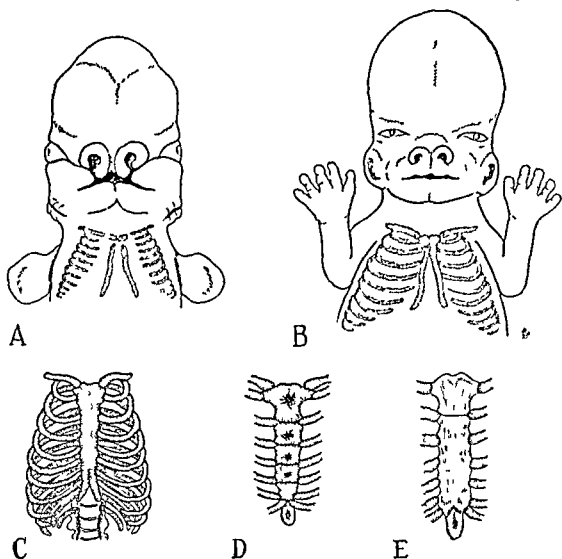


FIG 162 Diagrams showing development of the sternum. A, During sixth week (Adapted from William Patten) B, During eighth week (Adapted from William Patten) C, During ninth week (Adapted from Charlotte Müller) D, At five and a half months (University of Michigan Coll., EH 221) E, Adult (Adapted from Morris "Human Anatomy")

their course of development is, nevertheless, sufficiently similar so that we need not discuss them separately.

Once it starts, the development of the appendicular skeleton progresses very rapidly. Early in the sixth week only vaguely outlined concentrations of mesenchyme represent the primordia involved in the formation of the limbs and their girdles (Fig 155). Toward the end of the sixth week these pre-cartilage concentrations have become sufficiently molded so that some of the main bones are suggested (Fig 163, A, C). During the seventh week it begins

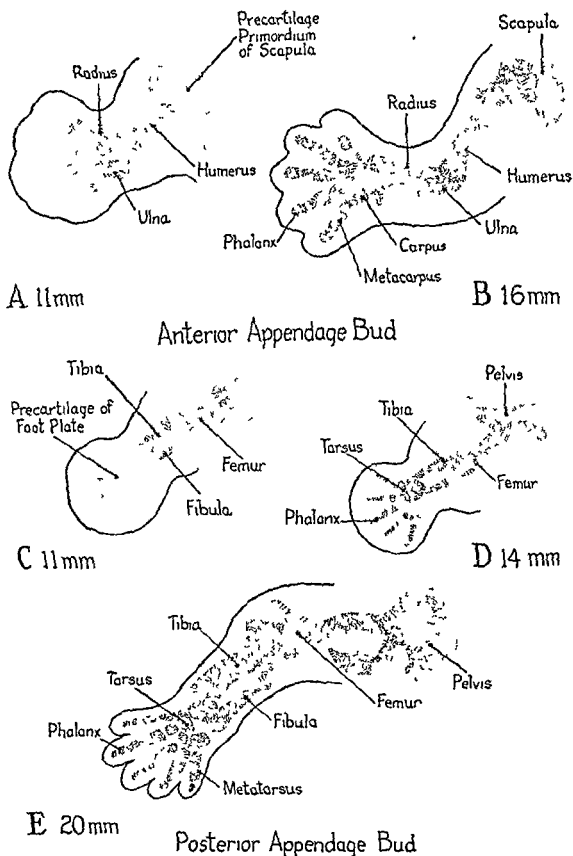


FIG 163 Early stages in development of the skeleton of the appendages (Modified from Bardeen and Lewis, *Am J Anat*, Vol 1, 1901) The fine stippling in the drawings of the younger stages indicates precartilag. concentrations of mesenchyme, the more sharply circumscribed and coarser stippling of the older stages represents cartilage

APPENDICULAR SKELETON

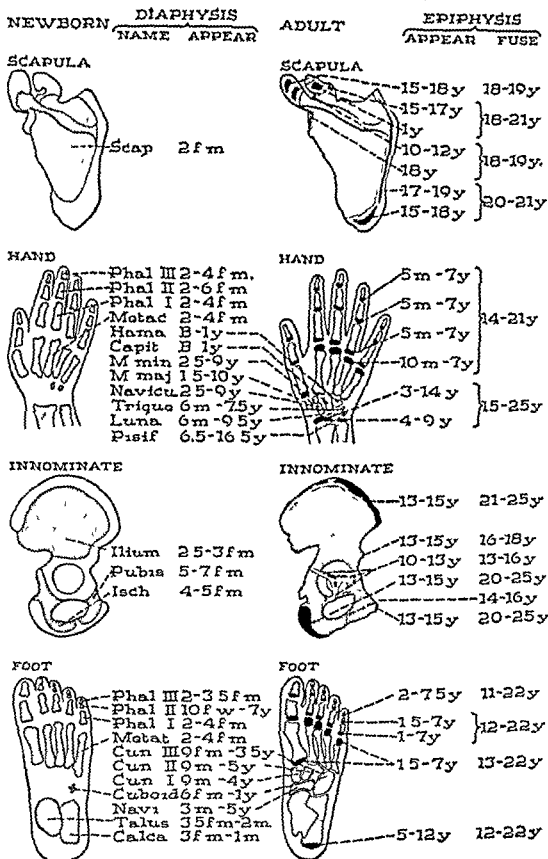


FIG 164 Graphic summary of the normal progress of ossification in development of the appendicular skeleton (After Graca and Noback, from Scammon in Morris "Human Anatomy")

to be possible to make out the primordia of many of the smaller bones of the hands and feet (Fig 163, B, D) and by the eighth week well-molded cartilage miniatures represent all the major parts of the appendages and girdles (Fig 163, E) In the eighth week, also, the primary ossification centers make their appearance in the major long bones of both the arm and the leg (Fig 172) The clavicle is already well advanced in ossification by the eighth week, being one of the earliest bones in the entire skeletal system to become calcified None of the other parts of either the pectoral or the pelvic girdle ordinarily show ossification until the ninth week By that time clearly marked centers are developed in both the scapula and the ilium (Fig 173)

It would carry us beyond the scope of this book to follow the later development of all the various bones in detail Fig 164 presents for reference a graphic summary of the progress of ossification in the appendicular skeleton In the left-hand column are outlines of the parts as they appear in the newborn, with the locations of their primary ossification centers stippled in At the ends of the appropriate leaders the time of ossification is given In the right-hand column are the outlines of the adult skeletal parts with their primary ossification centers shown in stippling and their epiphyseal centers shown in black The ages at which the epiphyseal ossification centers appear are given in the column immediately to the right of the figures, and the ages at which the epiphyses fuse with the rest of the bone are given in the column at the extreme right

Development of the Skull In dealing with the development of the skull it is helpful at the outset to recognize its neural and visceral (branchial) components The neural portion supports and protects the brain and the sense organs In mammals this part of the skull is itself composite, consisting of the phylogenetically old cranial floor with which are associated the capsular investments of the sense organs, and a more recently added facial scaffolding and vaulted cranial roof In general the older basal portion is preformed in cartilage whereas the newer facial and roofing bones are formed intramembranously There is, however, so much fusion and overlapping of these parts as they become molded into a coherent whole that it is unwise to try to draw too sharp a distinction between them on the basis of endochondral or intramembranous origin

The visceral (branchial) portion of the head skeleton consists of reduced and modified remains of the supporting structures of the gill arches which are so well developed in primitive water-living ancestral types This part of the skull is from the first associated with food seizure (jaws) and respiration (gill arches) Interestingly enough, most of the parts of it which have been retained in mammals are still concerned with the same functions, although they are utilized under very different conditions when lung breathing has replaced gill breathing Under air-living conditions the sound-receiving mechanism evolves into a much more elaborate form with the conversion of the obsolescent proximal ends of the first two visceral cartilages into the ossicles that transmit sound vibrations from the eardrum, across the middle ear, to the receptors of the

inner ear. Now, also, in the mammalian skull is the palatal shelf which partitions off the oral and nasal cavities from each other. Mechanically the palate is important to the young mammal in its nursing, and to the adult in permitting thorough mastication of food without interference with breathing. With these points from the evolutionary history of the skull in mind we may turn our attention to its embryological development.

The earliest indication of skull formation in the young mammalian embryo is the concentration of mesenchyme about the notochord at the level underlying the hindbrain (Fig. 155). From this region the concentration extends under the more rostral parts of the brain. It thus forms a sort of floor for the

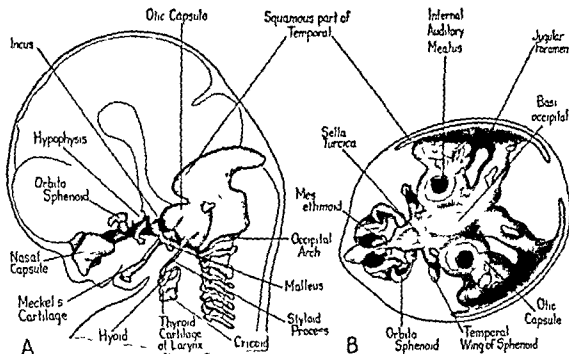


FIG. 165 The chondrocranium of a human embryo early in the eighth week of development (21 mm). A, Lateral view. B, Viewed from above. (Adapted from W. H. Lewis, *Carnegie Cont. to Emb.*, Vol. 9, 1920.)

developing brain and soon becomes converted into cartilage to constitute the beginning of the chondrocranium. As has already been suggested, the chondrocranium represents the oldest part of the brain-case phylogenetically, being reminiscent of the condition in primitive fishes of the shark type (Elasmobranchs) which had a skeleton composed of cartilage with no bone whatsoever. In such forms the skull consisted essentially of a cartilaginous cranial floor with the capsules of the olfactory organs added in front and the capsules of the eyes and ears laterally. Loosely associated with this primitive roofless chondrocranium of the Elasmobranchs was a well-developed gill arch (branchial) skeleton. It is interesting to see that the skull of a young human embryo first appears in the form of a cartilaginous cranial floor with nasal capsules rostrally, suggestions of orbital capsules laterally, and well-developed otic capsules on the sides farther caudally (Fig. 165). Moreover, there are cartilages associated with the young mammalian chondrocranium which un-

mistakably represent the gill-arch skeleton Meckel's cartilage (arch I), styloid process and lesser horn of hyoid (arch II), greater horn of hyoid (arch III), thyroid cartilage of larynx (arch IV), cricoid and arytenoid cartilages of larynx (arch V) (Figs 165, A, 169)

As is the case with other parts of the skeleton developing in cartilage, there is a tendency for the precartilage concentrations representing structures which arise in close association to run together into a common primordial mass. This we saw in the case of the vertebrae and ribs (Figs 156, 157), and the

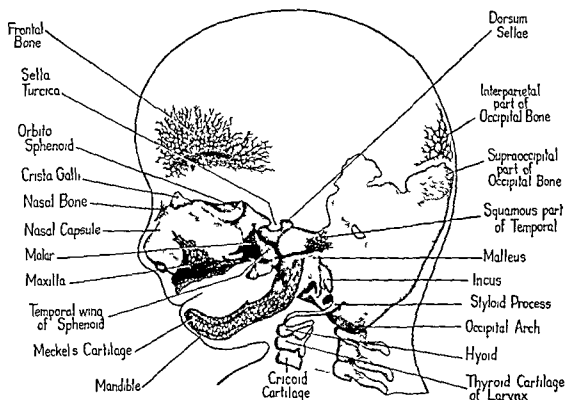


FIG 166 The developing skull of a human embryo of about nine weeks (38-40 mm). The drawing is a composite, based in part on the work of Macklin and in part on cleared preparations in the University of Michigan Collection. Cartilage is shown in gray wash, the locations of the endochondral ossification centers which have appeared at this age are indicated by superimposed stippling, the lacelike trabeculae of young intramembranous bone are shown in black.

appendicular skeleton (Fig 155). In the young chondrocranium it is quite apparent that there is confluence of primordial parts which will later become separate bones (see the regions specifically labeled in Fig 165). Not until the various ossification centers start in the chondrocranium do we have anything but the suggestions offered by the general shape and position of some part of the cartilage to help in the identification of the primordia of specific bones. Even the appearance of the ossification centers does not at once indicate either the configuration or the limits of the adult bone. For many of the bones of the mammalian skull are composite, having been formed by the fusion of bones that were originally separate in the lower animals. In such bones the ossification centers are multiple, since separate centers tend to appear in the regions representing bones that were originally independent. While it is not

feasible in a book of this sort to pursue these interesting correlations between comparative anatomy and embryology, we may briefly scrutinize the situation as to ossification in a few of the more important bones of the skull

The base of the skull in the mid-line is made up chiefly by three major bones (1) the occipital around the foramen magnum, (2) the sphenoid beneath the hypophyseal region of the brain, and (3) the ethmoid beneath the rostral part of the telencephalon and extending into the nasal region. The occipital bone exhibits four endochondral ossification centers—a median

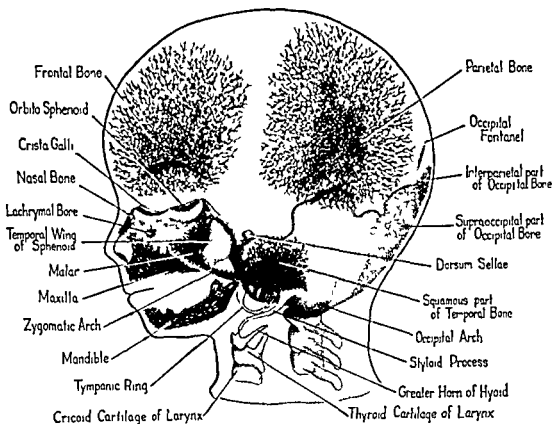


FIG. 167 The skull of a human embryo of about 12 weeks (80 mm). (Redrawn, with some modifications, from a reconstruction by O. Hertwig.) The scheme of representation is the same as that in the preceding figure with cartilage gray, endochondral ossification centers stippled, and membrane bone black.

center caudal to the foramen magnum (basioccipital), a median center, which in early stages is quadripartite, rostral to the foramen (supraoccipital), and a pair of centers one on either side of the foramen (the occipital arch, or exoccipital centers). In addition there are paired intramembranous centers which give rise to the part (interparietal) of the occipital bones above the superior nuchal line (Figs 166, 168, A). In studying alizarin-stained and cleared preparations it is interesting to note the contrast between the loosely arranged trabeculae of the young intramembranous interparietal center, and the much denser-appearing supraoccipital center of endochondral origin (Figs 173, 174). Of the ossification centers in the occipital bone the supraoccipital is usually first to appear (early in the ninth week) followed almost

immediately by the centers in the arch (exoccipitals) and the interparietals. The basioccipital center appears in the tenth week but in lateral views it is overlapped by the exoccipital centers and consequently not clearly defined. The fusion of these centers does not take place until long after birth (Fig. 171).

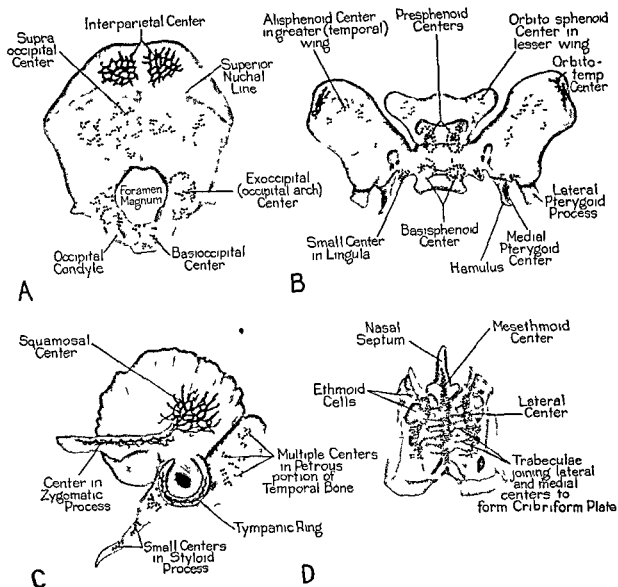


FIG. 168 Schematic diagrams showing location of ossification centers in four of the principal bones of the skull. Intramembranous centers are shown in black trabeculation, and endochondral centers in coarse black dots against shadowed diagram suggesting the adult shape of the bone. A, Occipital; B, Sphenoid; C, Temporal; D, Ethmoid.

The *sphenoid bone* shows five pairs of endochondral centers: a pair in the small wings (orbitosphenoids), a pair in the temporal or greater wings (alisphenoids), a pair in the more rostral part of the body of the sphenoid (presphenoid), a pair in the more caudal part of the body of the sphenoid (basisphenoid), and a pair in the lingulae (Fig. 168, B). There are also two pairs of intramembranous centers contributing to this complex bone. One of these pairs forms the outer, orbitotemporal portion of temporal wings, the other forms the medial lamina of the pterygoid process on either side (except the

hamulus) Some of these centers appear as early as the ninth week (temporal wings, Fig 166), others appear much later Even at the time of birth their coalescence is not complete, and the sphenoid bone is still in three parts The middle part is made up of the joined pre- and basisphenoid portions together with the orbitosphenoids The two lateral parts are composed chiefly of the temporal wings, and carry also the medial pterygoid plates

The cartilaginous *ethmoid* of the young chondrocranium consists of a medial, and paired lateral parts The medial portion (mesethmoid) extends

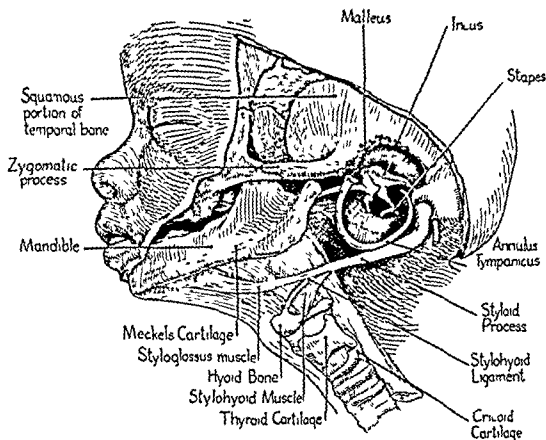


FIG 169 Dissection of head and neck of a fetus to show relations of Meckel's cartilage to developing ear ossicles (Modified from Kollmann)

to the tip of the developing nose Its more rostral part persists with little alteration as the cartilaginous part of the nasal septum (Fig 259) Ossification of its main portion gives rise to the perpendicular ethmoid plate which completes the nasal septum, and to the crista galli which projects medially above the cranial floor (Fig 320) The lateral ethmoidal cartilages start ossifying during the fourth month The trabeculae are delicate and widely spaced and lend themselves readily to remolding into the thin walls of the ethmoid cells and the formation of the delicate scroll-like turbinate processes supporting the superior and middle nasal conchae The medial and lateral ethmoidal cartilages are not at first joined to each other and the developing fibers of the olfactory nerve pass between them As development progresses cartilage bars bridging the medial cartilage to either lateral mass are formed among the nerve fibers (Fig 229, D) The cartilage soon becomes ossified and this region,

where the olfactory nerves go through many small foramina, is known as the cribriform plate

The *temporal bone* is formed primarily from the capsule of the inner ear which is part of the primitive chondrocranium (Fig 165) with the secondary addition of membrane bone (squamous part of temporal, Figs 166, 167) which forms a part of the ventrolateral cranial walls, and the styloid process from the

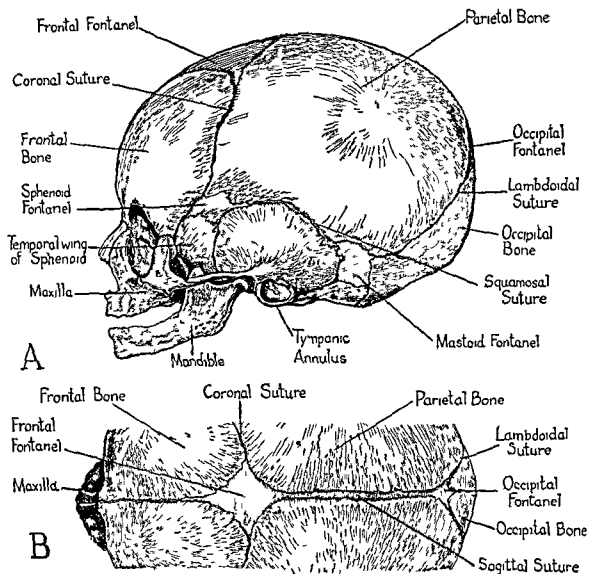


FIG 170 The skull at the time of birth (Modified from Morris "Human Anatomy") A, Lateral view B, Viewed from above

gill-arch skeleton The endochondral ossification centers in the ear capsule are named on the basis of their relations (opisthotic, prootic, pterotic, and epiotic) They appear in rapid succession during the latter part of the fifth and early in the sixth months, and soon merge, giving rise to the bony labyrinth encasing the internal ear within the so-called petrous portion of the temporal bone Paradoxically, the parts of the temporal bone which appear later in phylogeny calcify earlier in mammalian embryos Intramembranous ossification of the squamous portion and its associated zygomatic process is evident by the ninth week (Figs 166, 173), and during the tenth week the

SKULL

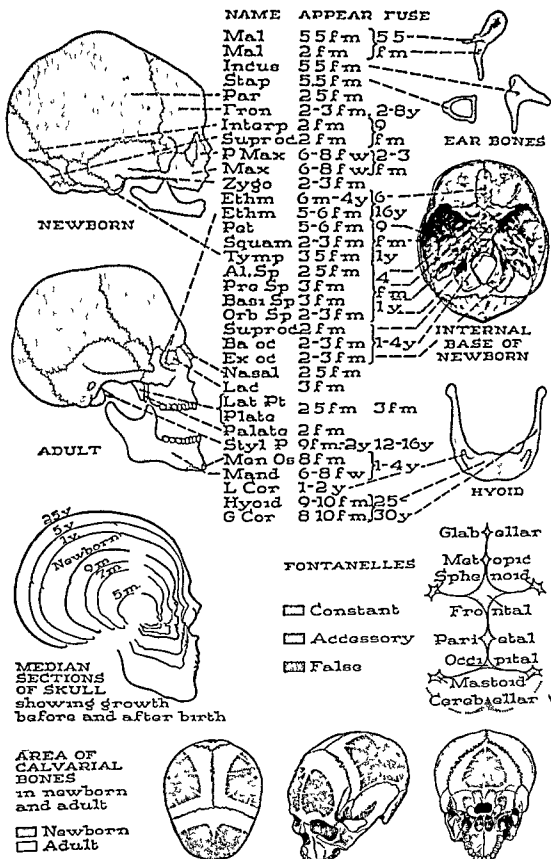


FIG 171 A schema of the development of the skull (After J G Graca and C R Noback, from Scammon, in Morris "Human Anatomy")

tympanic ring begins to ossify (Figs 168, C, 174) The styloid process of the temporal bone, as previously mentioned, is a modified remnant of the gill-arch skeleton (second arch) Of its two endochondral ossification centers, one appears before birth and the other in the second postnatal year

The formation of the membrane bones which constitute the sides and roof of the cranium is much easier to follow than the development of the bones constituting the base of the skull The frontal bone appears early in the ninth week in its characteristic position and expands rapidly (Cf Figs 166-167, 172-174) The parietal bone appears in the tenth week (Fig 174) By the time of birth these bones are in juxtaposition at the coronal sutures, but superiorly there is

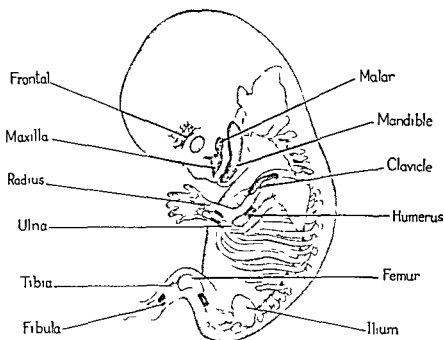


FIG 172 Human embryo of $23\frac{1}{2}$ mm (eighth week) stained with alizarin and cleared to show ossification centers Projection drawing ($\times 3$) by Jane Schaefer (University of Michigan Coll, EH 105)

still a wide gap (frontal fontanel) where the calvarium is incomplete (Fig 170) Posteriorly, the parietal bones have grown to meet the occipital bone along the lines of the lambdoidal sutures, but at birth here also there is still a median gap known as the occipital fontanel On the sides of the cranium there are two unclosed areas (the sphenoid fontanel just above the temporal wing of the sphenoid bone, and the mastoid fontanel just behind the squamous portion of the temporal bone) between it and the parietal bone superiorly and the occipital bone ventrally (Fig 170)

Except to note their very early appearance (seventh week) it will be more profitable to consider the development of the jaws and the palate in connection with the development of the teeth and other structures in the oral region Similarly, the portions of visceral-arch skeleton that are involved in the formation of the ear ossicles may best be considered at the time the development of the ear is discussed, and the portions of the visceral-arch skeleton associated

with the formation of the larynx may be taken up to better advantage in connection with the development of the respiratory organs

Detailed information on the time of fusion of the various ossification centers of which we have traced the first appearance and the early development best can be taken up when the adult skeletal system is studied. In all the standard

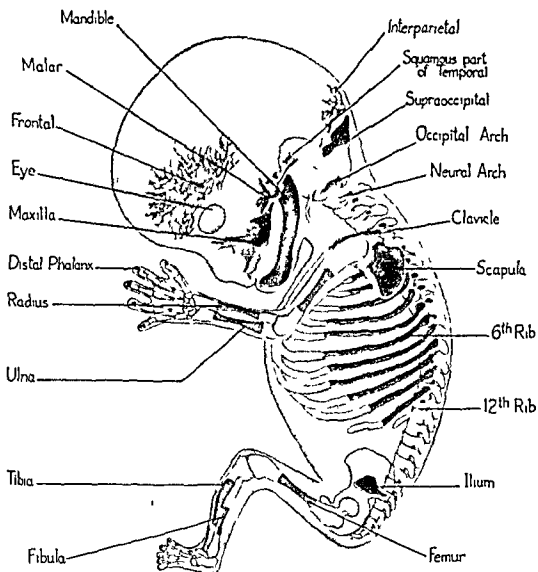


FIG 173 Human embryo of 39 mm (nine weeks) stained with alizarin and cleared to show the progress of ossification. Projection drawing ($\times 3$) by Jane Schaefer (University of Michigan Coll., EH 149)

medical text-books of human anatomy the times of the coalescence of the various centers are given in connection with the descriptions of each of the bones. Some of the major points as to the times of appearance and of fusion of the various centers are graphically summarized, for reference, in Fig 171

Progress of Ossification in Skeleton as a Whole Each of the more than 200 bones of the body has its own developmental history involving the formation of the connective tissue or the cartilage mass which precedes it, the appearance of local erosion centers if it be preformed in cartilage, number, location, and time of appearance of ossification centers, growth in length and diameter,

development of epiphyses, time of fusion of epiphyses and diaphysis, and finally the development of muscle ridges and articular facets. It would be neither possible nor desirable in a book of this sort to attempt any systematic

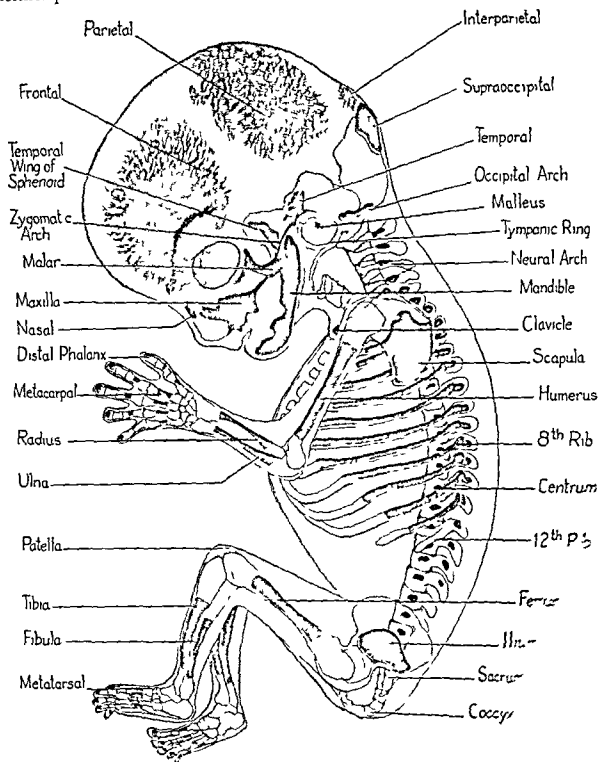


FIG 174 Human embryo of 49 mm (tenth week) stained with alizarin and cleared to show the developing skeletal system. Projection drawing (X 31). Jane Schaefer (University of Michigan Coll., EH 70)

survey of the development of all, or even the majority of the bones. What we have done has been to select certain types of bones and certain body areas and scrutinize the general trends of their development. If this approach

with the formation of the larynx may be taken up to better advantage in connection with the development of the respiratory organs

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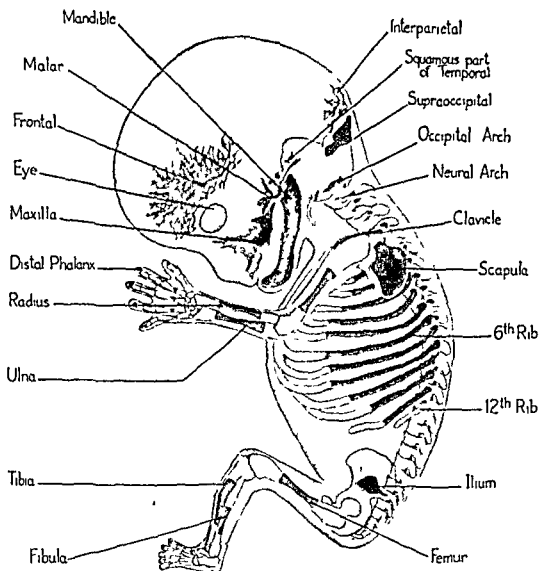


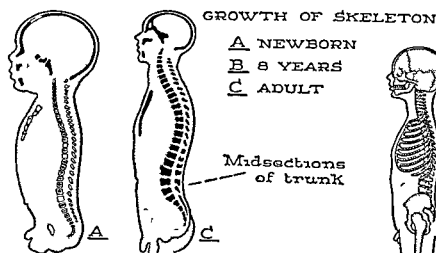
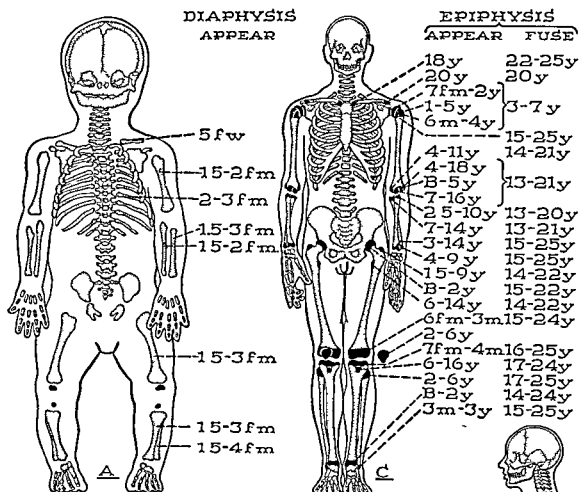
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SCHEMA OF OSSIFICATION OF THE SKELETON

TOTAL SKELETON



LEGEND

fw = Fetal weeks
 fm = Fetal months
 m = Postnatal months
 y = Years



FIG 176 A schema of the general development of the skeleton (From Scammon, in Morris "Human Anatomy," after J G Graca and C R Noback)

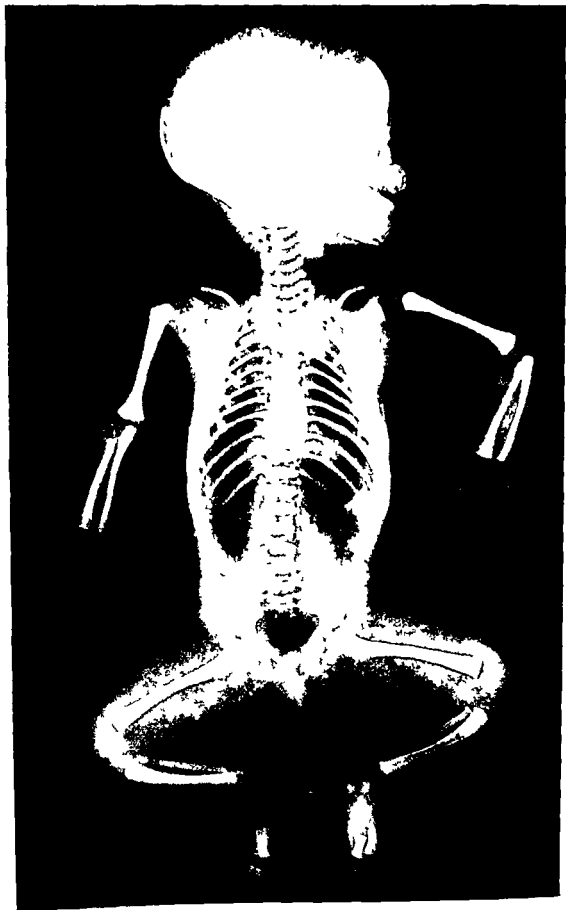


FIG 175 Skeleton of a fetus of the eighth month as shown by an x ray photograph, reproduced approximately one-half life size (From Cunningham "Anatomy," courtesy of Prof J C Brash and Dr E B Jamison)

and syndactyly (Fig 128, K-N), and in such fusions of the appendages as sirenomelia (Fig 126, C) The extent to which the skeleton is involved in defects such as amelia and phocomelia (Fig 127) is self-evident Very striking is the way in which many of the defects involving the extremities are transmitted by heredity (Fig 129)

Other defects of the skull and of the vertebral column such as cranioschisis and spina bifida in which the central nervous system is likely to be involved are treated in the chapter on the nervous system

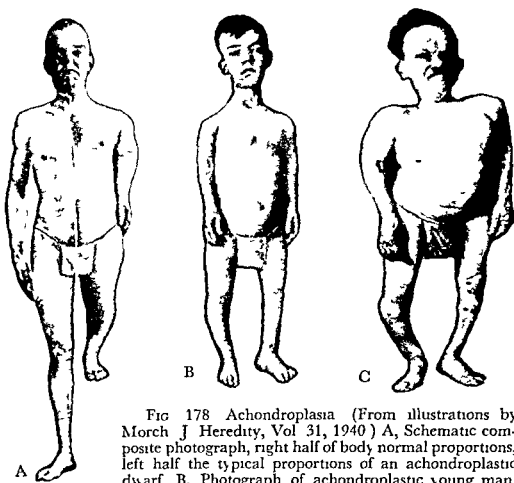


FIG 178 Achondroplasia (From illustrations by Morch J Heredity, Vol 31, 1940) A, Schematic composite photograph, right half of body, normal proportions, left half the typical proportions of an achondroplastic dwarf B, Photograph of achondroplastic young man C, Father of the young man shown in B

A very striking abnormality which affects the proportions of the long bones, rather than causing their gross distortion or their failure to develop, is known as chondrodystrophy or achondroplasia This is a condition in which there is a disturbance interfering with the increase in length of the long bones of the appendages by growth at the epiphyses In such individuals the head and body, in striking contrast with the appendages, develop in perfectly normal proportions (Fig 178, A) Other than the obvious involvement of epiphyseal growth, the exact mechanism of the disturbance is not well understood It seems probable that it is due to a gene defect for it exhibits a strong tendency to be directly transmitted by heredity (Fig 178, B, C)

has been successful it should have provided the student with sufficient background to look up with understanding the details of development for any of the parts of the skeleton in which he may become particularly interested

In addition to information on specific bones it sometimes becomes desirable to know the state of development exhibited by the skeleton as a whole. It might, for example, be important medicolegally to establish the age of a fetus too badly preserved, or too fragmentary, to permit reliance on any of the ordinary means of determining age. Most helpful under such circumstances is some graphic summary which will give at a glance the state of development of the skeleton as a whole. In the early stages of development the best type of

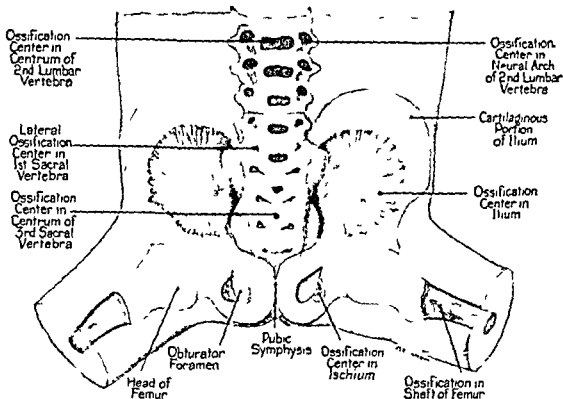


FIG. 177 Pelvic region ($\times 2\frac{1}{2}$) of human embryo of fifteenth week, stained with alizarin and cleared to show the ossification centers (University of Michigan Coll., EH 126, 130 mm C-R)

preparation for such a purpose is one in which an embryo is so treated that it becomes transparent. Particularly if such material is stained with alizarin the ossification centers will stand out very clearly. The best results with embryos of the first three months are obtained by clearing in potassium hydroxide and glycerin (Figs 172-174). This method does not work as well with older embryos and recourse must be had to clearing in oil of wintergreen by the Spalteholz method or one of its modifications, or to x-rays (Fig 175). Study of Figs 172-175 and 177 will give a good visual summary of the progress of development in the skeleton as a whole. Fig 176 gives ossification and fusion times for a number of skeletal parts not covered elsewhere.

Abnormalities of Skeletal Development Many of the abnormalities that may involve the skeletal system have been touched upon already in other connections. We have seen the nature of the skeletal distortions in polydactyly

and syndactyly (Fig 128, K-N), and in such fusions of the appendages as sirenomelia (Fig 126, C) The extent to which the skeleton is involved in defects such as amelia and phocomelia (Fig 127) is self-evident Very striking is the way in which many of the defects involving the extremities are transmitted by heredity (Fig 129)

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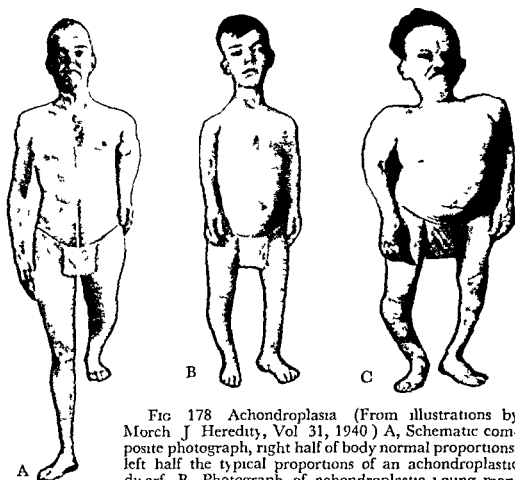


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I I

The Muscular System

The muscular system is composed of specialized cells or fibers in which the function of contractility has been highly developed. On the basis of differences in their microscopical structure, three types of muscle are recognized (1) Smooth muscle, found characteristically in the walls of the hollow viscera, ducts, and blood vessels, (2) cardiac muscle, found only in the walls of the heart, and (3) skeletal muscle, which as the name implies is attached to, and serves to move, the bony framework of the body. Before considering the development of the architectural plan of the muscular system, let us first take up the histological changes involved in the differentiation of the three types of muscle which are its structural units.

HISTOGENESIS OF MUSCLE

Smooth Muscle With the minor exceptions of the sphincter and dilator muscles of the pupil of the eye, and the peculiar contractile cells in the walls of the sudoriferous glands which are probably of ectodermal origin, smooth muscle arises from the mesoderm. At a very early stage of development, wandering mesenchymal cells concentrate about the epithelial linings of such structures as the gut tube, or the urogenital ducts, or the large vascular channels. As these mesenchymal cells become arranged in the zones in which involuntary muscle is destined to develop, they tend to lengthen in the direction in which their contractile power will be exerted (Fig. 278). By the sixth or seventh week fibrils can be made out running lengthwise in the cytoplasm of the young smooth muscle cells (Fig. 179, A). These are the so-called myofibrils¹ which are believed to be the contractile elements within the muscle cells.

By the ninth week the characteristic spindle shape of the smooth muscle elements is well established and the myofibrils have become more numerous and more delicate (Fig. 179, B). During the latter part of gestation there is little striking change in the character of smooth muscle cells although the

¹ It should perhaps be emphasized that myofibrils are not demonstrable by ordinary means in undisturbed living muscle. They show up clearly only after the cells have been subjected to injury or to the coagulation processes involved in fixation. This should not be taken as proof that no such things as myofibrils exist in living muscle. Theoretically at least, they might be present but invisible because of lack of any optical qualities which differentiate them from the surrounding cytoplasm. More work with some of the newer methods of study is needed on the nature and action of these interesting fibrils which, in one form or another, seem to be characteristic of all types of muscle.

increase in the number of myofibrils continues, and the cells become somewhat more robust (Fig 179, C)

Cardiac Muscle In the formation of the primitive tubular heart it will be recalled that the splanchnic mesoderm gives rise to the epimyocardial layer which invests the endocardial primordia (Fig 72) The surface cells of the epimyocardium retain their original epithelial character, forming the mesothelial covering of the heart The inner part of the epimyocardium, as its name implies, gives rise to the muscular tissue of the cardiac wall In the early stages of their differentiation, the cells of the myocardium are packed closely to-

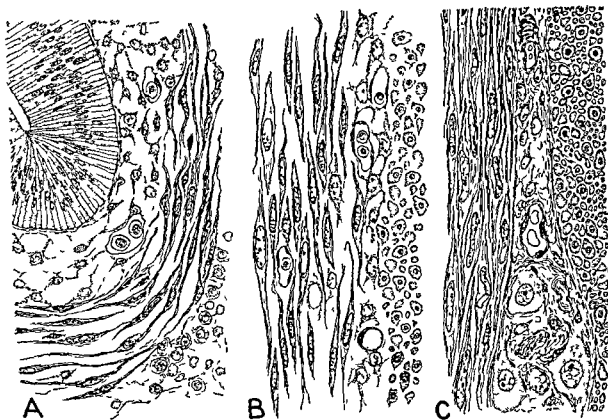


FIG 179 Histogenesis of smooth muscle (Camera lucida drawings, $\times 500$)
 A, Intestinal wall of 14.8-mm embryo B, Small area of tunica muscularis of intestine of 33-mm embryo C, Small area of tunica muscularis of adult small intestine, including part of a ganglion of the myenteric plexus

gether with little indication of any definite plan of arrangement About the time the first contractile activity begins, the nuclei are somewhat less close together and the cytoplasm of adjacent cells has coalesced to form a loose, irregular syncytium (Fig 180, A) It is at about this time, also, that a suggestion of myofibril formation begins to be recognizable

Not long after their first appearance the young myofibrils become very conspicuous They are much larger than the fibrils of more mature cardiac muscle and show conspicuous dark bands due to the local concentration of anisotropic substance (Fig 180, B) At this early stage the myofibrils are relatively few in number and they pursue a startlingly irregular course, frequently crossing one another They traverse the syncytium for considerable distances,

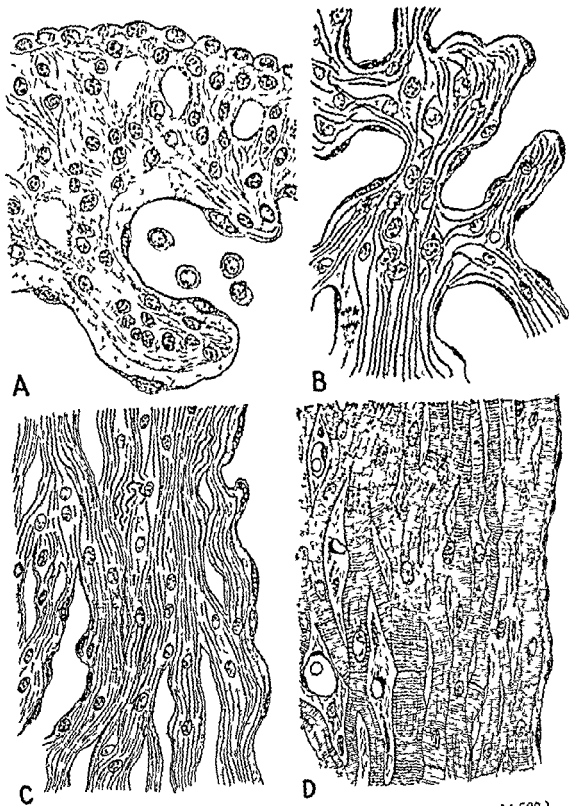


FIG 180 Histogenesis of cardiac muscle (Camera lucida drawings, $\times 500$)
 A, Entire thickness of ventricular wall of 4.5 mm embryo B, Developing trabeculae from inner part of ventricular wall of 9 mm embryo C, Inner part of ventricular wall of 45 mm embryo D, Inner part of adult right ventricular wall

certainly not being restricted to any limited cytoplasmic areas such as might have been derived from single cells before their coalescence

As the growing muscle is pulled into spiral bands about the developing chambers of the heart, the strands of the syncytium gradually become less irregular in their arrangement. In sectioned material from the hearts of embryos of the third month, areas appear showing groups of fibers running more or less parallel to each other and crossing other fiber groups at varying angles. The myofibrils have become more abundant, and lining up of the dark and light portions of adjacent fibrils is beginning to give the muscle a cross-striated appearance (Fig 180, C). In comparing fetal with adult cardiac muscle the further increase in the number of myofibrils and their decrease in coarseness is most striking (Cf C and D in Fig 180.)

The last of the characteristic histological features of cardiac muscle to make their appearance are the intercalated disks. These are curious transverse markings which seem to appear about where one could readily believe adjacent cellular elements fused to form the syncytium, but with cardiac muscle having been syncytial almost from its establishment, the conception that these disks really do represent the re-emergence of the original cell boundaries is difficult to support.

Skeletal Muscle Except for the cephalic region, and possibly the distal parts of the appendages, the skeletal muscles of the body are derived from the myotomal portions of the mesodermic somites (Fig 63). The muscles of the head, and some of the neck muscles, are formed by mesenchymal cells from the branchial arch region and from the more dorsally located mesenchyme of the cephalic regions rostral to the otic level. It will be recalled that in mammalian embryos the most cephalic somites appear just caudal to the otic vesicle (Fig 182). In many of the lower forms, however, definite preotic somites are formed, and it seems quite probable that the more dorsally located portion of the cephalic mesenchyme of mammals represents what, earlier in phylogeny, was segmentally arranged dorsal mesoderm, serially homologous with the somites farther back in the body. The fact that the eye muscles, which are derived from this cephalic mesenchyme, are innervated in a manner similar to somatic muscles derived from typical postotic mesodermic somites offers strong collateral evidence in favor of such an interpretation.

The mesoderm of the young appendage buds is difficult to analyze because the entire central part of the bud is composed of densely packed mesenchyme without any lines of demarcation helpful in determining its source, and even without any indication, at first, as to what will form skeletal parts and what will form muscle. Again, on the basis of findings in lower forms, it seems probable that the part of the mesoderm in the appendage buds which gives rise to the muscle represents outgrowths from the myotomes at appendage-bud levels (Fig 182). Certainly the innervation of the appendages points strongly to such an interpretation.

The histological changes involved in the formation of skeletal muscle are the same regardless of whether it is of primary myotomal origin or from mesen-

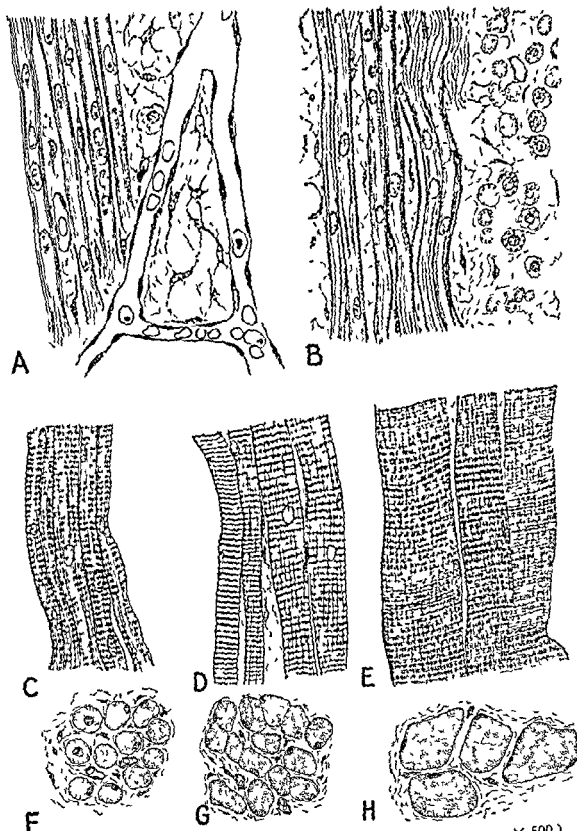


FIG 181 Histogenesis of skeletal muscle (Camera lucida drawings, $\times 500$)
 A, From 32-mm embryo B, From 45-mm embryo C, From 200 mm embryo
 D, From term fetus E, From adult diaphragm F-H, Transversely cut muscle
 fibers drawn from the same material and to the same scale as the longitudinal
 sections directly above them

chymal tissue of similar potentialities. The cells early show a tendency for their finely granular cytoplasm to become elongated. At first the young muscle fibers possess only a single, large, centrally located nucleus. This condition, however, persists for only a brief period and with their greater elongation the fibers become multinucleated (Fig 181, A).

Myofibrils become recognizable coincidentally with the elongation of the young muscle fibers. The myofibrils are at first few in number and, as was the case with smooth and cardiac muscle, much coarser than the myofibrils of adult muscle. Almost from the first they show alternating dark and light bands due to local serially repeated concentrations of anisotropic substance. The myofibrils first appear in the peripheral part of the developing fiber, leaving a central core of unmodified cytoplasm in which the nuclei are located (Fig 181, A, B).

As differentiation of the muscle fibers progresses, the myofibrils become more abundant and more slender. They tend to fill the central cytoplasmic area and, during the last third of intra-uterine life, begin to crowd the nuclei toward the periphery of the fibers (Fig 181, F, G). At the same time the juxtaposition of the dark and light zones of adjacent myofibrils gives the muscle fiber as a whole a cross-banded appearance (Fig 181, C). This cross-banding is much more conspicuous in skeletal than in cardiac muscle and is responsible for the fact that skeletal muscle is often designated as striated voluntary muscle.

In a fetus at term the skeletal muscle fibers have all the essential histological characteristics of adult skeletal muscle. The fibers are, however, much more slender than those of the adult and the nuclei are more rounded and less strongly crowded against the sarcolemma. The anisotropic (dark) bands are somewhat less prominent in fetal than in adult muscle so that it gives the impression of having more delicate striations. (Cf Fig 181, D, E).

MORPHOGENESIS OF THE MUSCULAR SYSTEM

From the functional standpoint, and on the basis of differences in the character of their innervation, the muscles of the body fall into one or the other of two categories—the visceral musculature or the skeletal musculature.

VISCERAL MUSCULATURE

The visceral musculature arises from *splanchnic mesoderm* that in the course of development applies itself as an outer coat around the primary epithelial lining of hollow internal organs. Except for the musculature of the heart, which is of its own peculiar type, the visceral musculature is *smooth*. All of the visceral musculature, whether cardiac or smooth, operates under the regulatory control of the autonomic nervous system, but can not be made to respond directly to our will. The plan of arrangement exhibited by this involuntary musculature is definitely correlated with the function of the particular organ in which it occurs and is, therefore, best considered in connection with the discussion of the several organ systems in subsequent chapters.

In general, the muscle cells are organized into bands or sheets held in place within the organ by connective tissue. In tubular organs such as those of the digestive system where semisolid contents are moved through the lumen there are characteristically two coats of smooth muscle, an inner circular and an outer longitudinal. It is the co-ordinated action of these two muscle layers which is responsible for the propulsive action known as peristalsis. In organs such as the urinary bladder, or the uterus, or the ventricular chambers of the heart in which contraction of the walls expels the contents and reduces the lumen to a mere potential slit, the muscle tends to be arranged in irregularly interlacing bands. The force of contraction in such a system pulls the walls in from all directions, thus affording the most efficient mechanism possible for complete reduction of the lumen with the resultant expulsion of its contents.

SKELETAL MUSCULATURE

Skeletal muscle fibers, acting under the control of the will, attach to and move the bony framework of the body, take part in the formation of the walls of the oral, thoracic, abdominal, and pelvic cavities, and are built into the structure of the pharynx, larynx and upper esophagus, and the eyes and ears. Altogether, the skeletal musculature of the adult body composes some 40 to 45 per cent of its total weight. Except for a few small, circularly disposed muscles such as the orbicularis oris, or the muscle in the upper part of the esophagus, or the anal sphincter, the skeletal muscles tend to be organized masses of characteristic shape, circumscribed by connective-tissue sheaths, and exhibiting definite points of origin and of insertion. Our text-books of human anatomy recognize some 327 paired and two unpaired skeletal muscles in the adult body. Any attempt to consider systematically the development of such an array of muscles would be entirely beyond the scope of this book. We can, however, see what the simple basic plan of the primordial muscle masses is like in young embryos, and try to follow in broad outline some of the developmental trends, an understanding of which will prove helpful in studying adult myology.

Primary Arrangement of Myotomes in Young Embryos It will be recalled that the first somites to be formed are the most cephalic ones of the series and that they appear close behind the auditory placode during the third week of development (Fig. 48). Their number is increased rapidly by the addition of new somites caudal to those already formed (Figs. 49-53), until, by the sixth week, their total has reached about 39 pairs (Fig. 60). Some uncertainty as to the exact count exists because of the difficulty of assessing the segmental value of the mesodermal primordia of the eye muscles, and on account of the variable number of poorly defined somites in the rudimentary caudal region. Surprisingly constant are the eight cervical, twelve thoracic, five lumbar, and five sacral somites. Adding to these 30 the usual four occipital and five caudal myotomes gives the 39 pairs of somites indicated in the conventionalized diagram of Fig. 182. Such a count of course leaves out of consideration the problematical eye-muscle primordia.

The stippled areas in Fig 182 indicate approximately the extent of the myotomes when they first differentiate (Cf Fig 63, C) The unstippled ventral extensions from these areas suggest schematically the general territory of the embryonic body into which each myotome extends The developing muscle fibers in the myotomes at first run in a craniocaudal direction In certain areas the primordial muscle masses, as we shall see directly, undergo changes in their fiber direction and extensive secondary shifting out of their areas of origin, but many of the trunk muscles, especially the intercostal muscles and the muscles of the vertebral column, retain essentially their original segmental relations Even in regions where the changes in the relations of the muscles themselves are difficult to follow, the cutaneous nerves still exhibit a distribution which gives a striking demonstration of the areas of the adult body which are derived from the several segmental zones of young embryos (Cf Figs 182, 183, 199) The innervation of the various primordial muscle masses is acquired very early from nerves arising at the same segmental level in the body so that when secondary changes in the position of the muscle occur the already attached nerve is pulled along with the muscle The level of origin of a muscle is, therefore, indicated by the segmental level at which the nerve supplying it arises Moreover, the path of the nerve in reaching the muscle suggests the path followed by the muscle in arriving at its adult location A good example of this sequence of events is the association of the phrenic nerve with the muscle of the diaphragm Its almost direct course from the fourth and fifth cervical nerves of the young embryo to the developing diaphragm is clearly shown in Fig 199 In striking contrast is its long course in the adult from the neck, along the pleuropericardial folds, to the diaphragm in the position it finally comes to occupy in the body far caudal to the segmental level of its origin

Fundamental Processes in Differentiation of Muscular System With the primitive segmental plan of the neuromuscular system of young embryos clearly in mind as a starting point, it is possible to see certain commonly repeated types of changes which are operative in establishing the adult plan of arrangement of the muscles These have been ably characterized by McMurrich under the six headings which are given below with only slight changes from his original order and phrasing

1 There may be changes from the original craniocaudal direction of the muscle fibers in the myotomes This is a trend of very widespread occurrence As a matter of fact, the original direction of the fibers is retained in comparatively few of the adult muscles An excellent example of directional change is afforded by the oblique course of the muscles of the abdominal walls (Figs 186, 187)

2 A longitudinal splitting into two or more portions may occur in an originally single primordial muscle mass This process is well illustrated in the formation of the trapezius and sternomastoid (Figs 189, 190, 192)

3 There may be tangential splitting of the original myotomal masses into two or more layers An example of this process is afforded by the manner of

In general, the muscle cells are organized into bands or sheets held in place within the organ by connective tissue. In tubular organs such as those of the digestive system where semisolid contents are moved through the lumen there are characteristically two coats of smooth muscle, an inner circular and an outer longitudinal. It is the co-ordinated action of these two muscle layers which is responsible for the propulsive action known as peristalsis. In organs such as the urinary bladder, or the uterus, or the ventricular chambers of the heart in which contraction of the walls expels the contents and reduces the lumen to a mere potential slit, the muscle tends to be arranged in irregularly interlacing bands. The force of contraction in such a system pulls the walls in from all directions, thus affording the most efficient mechanism possible for complete reduction of the lumen with the resultant expulsion of its contents.

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6 Finally there may be degeneration of portions, or of the whole, of a muscle segment. When a muscle thus degenerates, it tends to become converted into connective tissue, and many of the strong aponeurotic sheets which occur in the body owe their origin to this process. Thus, for example,

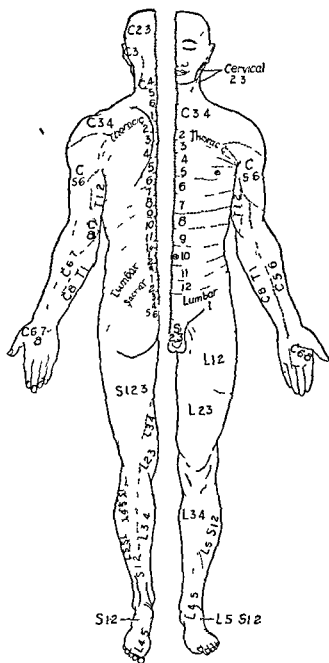


FIG 183 Segmental areas of the adult body as indicated by distribution of cutaneous nerves (Adapted from various sources) Compare with Fig 182

the aponeurosis connecting the occipital and frontal portions of the occipitofrontalis muscle in man is formed in this way. In such forms as the lower monkeys this complex remains almost entirely muscular. Another good example is to be found in the aponeurosis which occupies the interval between the superior and inferior serrati postici, these two muscles being continuous

formation of the two oblique, and the transverse layers of the abdominal walls, and by the intercostal muscles (Figs 184, 186, 187)

4 Another process of frequent occurrence is the fusion of portions of successive myotomes to form a single muscle. This is well illustrated by the rectus abdominis muscle which is formed by the fusion of the ventral portions of the last six or seven thoracic myotomes (Fig 187). The superficial portions of the sacrospinalis arise in a similar manner.

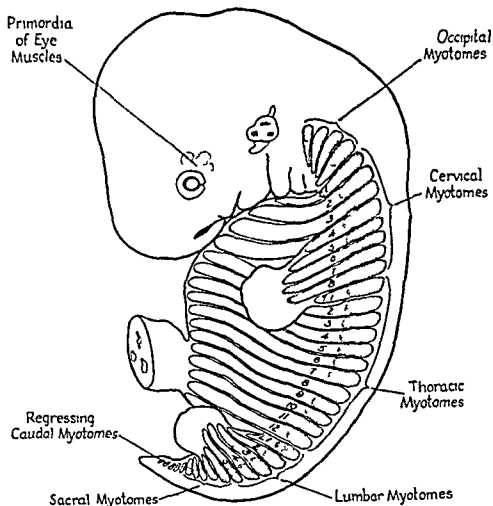


FIG 182 Schematic diagram showing the regions into which the embryonic myotomes extend. The stippled area indicates the approximate size of the original mesodermic somite, the unstippled ventrolateral areas outlined opposite each somite suggest the territory into which the myotomes tend to extend. Compare with Fig 183.

5 There may be a migration of muscle primordia, wholly or in part, to segmental levels different from those of their origin. For example, the latissimus dorsi which arises from cervical myotomes (Fig 186) extends far caudad (Fig 187) and finally attaches to the lower thoracic and lumbar vertebrae and the crest of the ilium. The muscles of facial expression exhibit an equally striking example of migration away from the segmental level of origin—in this case from the region of the second visceral arch cephalad to positions around the mouth, nose, and eyes (Figs 189–193).

fusion of myotomal fibers to form massive suprasedgmental muscles is furnished by the development of the sacrospinalis muscle group (Figs 186, 187) From their position dorsal to the axial skeleton these muscles are frequently characterized as epaxial trunk muscles (Fig 185) Ventral to the vertebral column,² other long muscles are formed by a similar process Such muscles (e g, the psoas major and quadratus lumborum) are spoken of as hypaxial trunk muscles

The muscles of the lateral and ventral walls of the abdomen arise from the lower thoracic and upper lumbar myotomes In 9-10 mm embryos ventral extension of these myotomes is already well advanced, but the original cephalocaudal direction of the fibers is still clearly retained (Fig 184) Fusion of

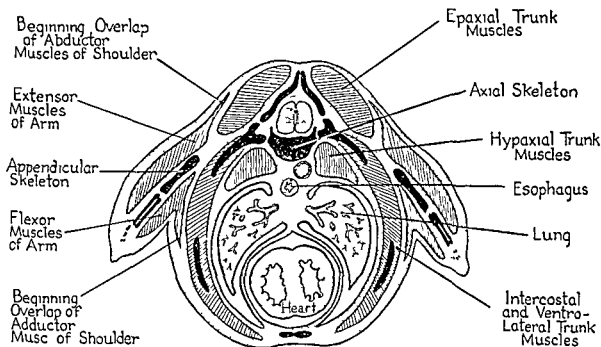


FIG 185 Schematic diagram of some of the major developing muscle masses to show their relations to the axial, and to the appendicular skeleton

the developing fibers of adjacent myotomes has commenced and is particularly well marked along the ventral borders of the growing myotomes where it foreshadows the formation of the rectus abdominis muscle (Cf Figs 184, 187) In embryos of about 5 weeks (Fig 186) there is evident the beginning of the tangential splitting of myotomes to form the deep and superficial muscle layers with their fibers running in different directions The characteristic angle of the external oblique fibers, the way they become continuous so that the old myotomal boundaries are no longer evident, and their separation from the rectus abdominis fibers, are all clearly shown in reconstructions of embryos at the beginning of the eighth week (Fig 187)

Even this very sketchy account of some of the main steps in the development of the muscles of the trunk and body-wall should make it apparent that

² In the lumbar region where the ribs do not form a clear cut boundary, the transverse processes of the vertebrae are regarded as indicating the line of demarcation between epaxial and hypaxial trunk muscles

in lower forms. The strong lumbar aponeurosis and the aponeuroses of the oblique and transverse muscles of the abdomen also arise by such a process.

Having become familiar with the fundamental trends involved in the development of the muscular system as a whole, we may now consider briefly a few arbitrarily selected regions where the development of the musculature will illustrate the principles outlined.

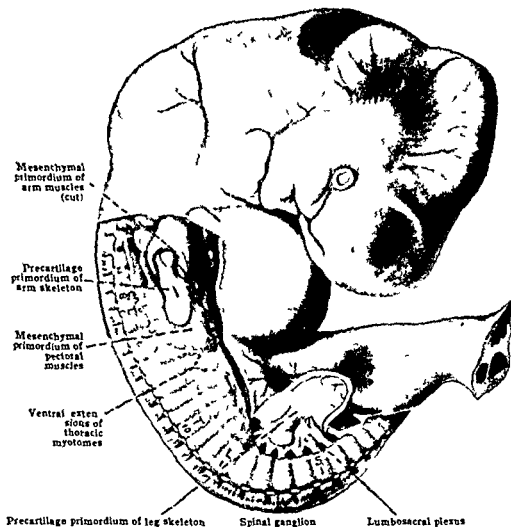


FIG. 184 Superficial dissection ($\times 125$) to show developing trunk muscles of a 9-mm human embryo (After Bardeen and Lewis, *Am J Anat*, Vol 1, 1901)

Muscles of Trunk and Body-wall The more dorsal and deeper parts of the myotomes of the trunk tend to retain their segmental character with least modification. Here they lie closely interdigitated with the developing axial skeleton and become attached to it as the intervertebral muscles. In the deeper parts of the ventrolateral extensions of the myotomes at thoracic levels, also, the original segmental arrangement is kept in the form of the intercostal muscles. At the same time tangential splitting of the myotomes tends to separate off some of their more superficial parts which become much more modified than do the deeper layers. These superficial muscle masses give rise to the long muscles of the neck and back. One of the best examples of the end-to-end

muscles developing on the originally dorsal aspect of the appendage become the extensors while those developing ventrally become the flexors (Fig 185). Outgrowths of the dorsally situated mesodermal masses toward the trunk furnish the primordia from which abductor muscles arise and similar ventral

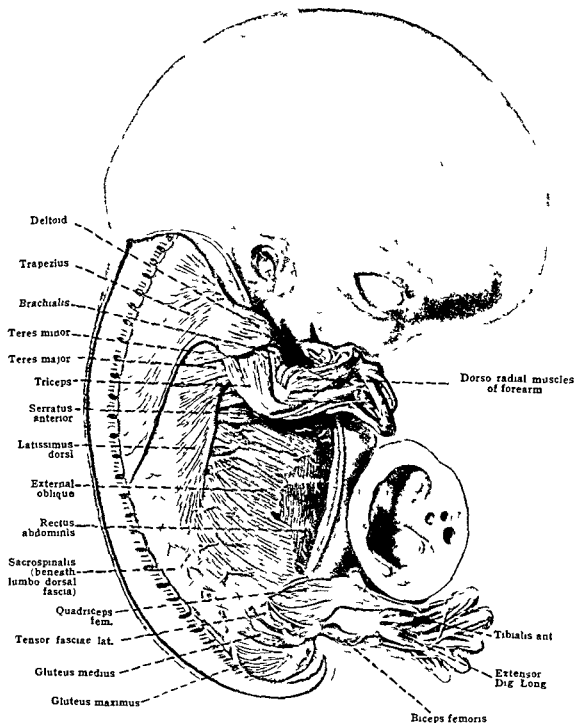


FIG 187 Superficial dissection ($\times 75$) to show developing trunk and limb muscles of a 20 mm human embryo (After Bardeen and Lewis, *Am J Anat*, Vol 1, 1901)

outgrowths give rise to the adductor muscles (Fig 185). Later in development, because the arm and leg flex and rotate differently out of their originally similar positions, the extensor muscles of the arm come to lie on its outer and dorsal aspect while the corresponding muscles of the leg lie on its ventral and

the general trends referred to in the preceding section do not operate independently but in various combinations. Thus in the case of development of the abdominal muscles, tangential splitting into superficial and deep layers, change of fiber direction, fusion of adjacent myotomes, and formation of aponeuroses by fibrous replacement of certain muscle areas were all involved.

Muscles of Appendages The difficulty of tracing in mammalian embryos the precise origin of the muscle-forming mesoderm of the appendage buds has

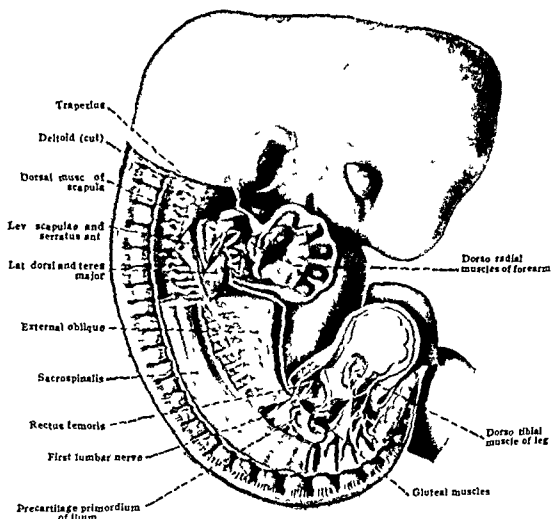


FIG 186 Superficial dissection ($\times 10$) to show the developing trunk and limb muscles of an 11-mm human embryo (After Bardeen and Lewis, *Am J Anat*, Vol 1, 1901)

already been mentioned. The innervation of this muscle, however, is so similar to that of other muscle masses unequivocally of somitic origin that—at least until evidence to the contrary is forthcoming—we may regard the primordial muscle masses of the appendage buds as representing outgrowths from the group of myotomes at the segmental levels at which the arm and the leg arise (Fig 182).

As the bones of the appendicular skeleton become differentiated, the mesoderm from which the muscles will take shape tends to aggregate in masses grouped dorsal to, or ventral to, the developing skeletal parts. In general the

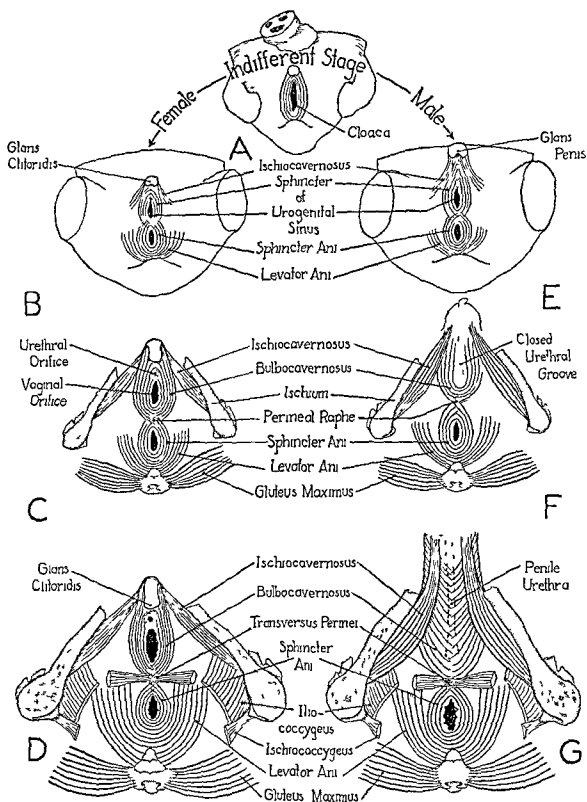


FIG 188 Schematic diagrams showing some of the steps in the development of the perineal musculature in the two sexes (Based, in part, on the work of Popowski Anat Heite, Bd 12, 1899)

inner surface (See pp 193-195 and cf Figs 185, 186, 187) Embryos of the eighth week (Fig 187) are particularly instructive in this connection for the major muscles familiar in the adult are already becoming recognizable, while the limbs have not yet flexed and rotated so far out of their primary position that the corresponding muscle groups are difficult to recognize

Muscles of Perineal Region The muscles of the perineal region differentiate somewhat later than the abdominal musculature They appear to be derived from poorly defined mesodermal masses probably arising as ventral extensions of the third and fourth sacral myotomes At first the developing muscle fibers tend to encircle the primitive cloacal opening (Fig 188, A) With the partitioning of the cloaca into urogenital and rectal portions, the fibers become rearranged so that anus and urogenital sinus each have separate sphincter muscles (Fig 188, B, E) About the anal region, in both sexes, some of the more peripherally located fibers become organized into the levator ani muscles (Fig 188, B-D, E-G) The later differentiation of the muscle about the orifice of the urogenital sinus differs in the two sexes, although homologous muscle groups remain clearly recognizable In the female some of the more laterally located fibers become partially separated and organized to form the small ischiocavernosus muscles to the clitoris After the vagina becomes well developed, some of the inner fibers of the sphincter of the urogenital sinus become rearranged to constitute the urethral sphincter while the bulk of them form the bulbocavernosus muscles enclosing the vaginal orifice (Fig 188, B-D)

The homology of the ischiocavernosus muscles in the two sexes is readily apparent at any stage of development The changes in the relations of the bulbocavernosus fibers are more divergent In the male the original urogenital orifice lies in line with the urethral groove on the under side of the developing penis The closure of this groove to form the penile urethra carries the urogenital orifice out to the tip of the penis (Fig 381) With this change the bulbocavernosus fibers from either side are brought toward the mid-line beneath the cutaneous raphé marking the line of closure of the urethral groove (Fig 188, F) Casual scrutiny of the way these bulbocavernosus fibers in the adult male enwrap the proximal part of the penis makes their relations appear quite different from the corresponding muscles in the female Careful comparison of the manner of insertion of these fibers in the clitoris and in the penis, in the adult, and a review of their relations in embryos before closure of the urethral groove has occurred should, however, serve to make the homology apparent

Muscles of Head and Neck In young embryos the head is broadly attached to the trunk with the limits of the future cervical region ill defined Moreover, some of the muscles which make their first appearance in the zone of transition from head to trunk are carried caudad from their level of origin as they develop, whereas others move farther rostrad It is, therefore, more logical and convenient in a brief account such as this to deal with the development of the musculature in the cervicocephalic region as a whole

Between the point at which the eye muscles originate and the clearly recognizable postotic somites, the mesoderm at first consists merely of loosely scattered mesenchymal cells. These cells, however, multiply with great rapidity and soon become densely packed in all the otherwise unoccupied space between the developing brain and the superficial ectoderm. Laterally and ventrally, conspicuous masses of them are crowded into the visceral (branchial) arches. It is from this mesoderm that a large part of the musculature of

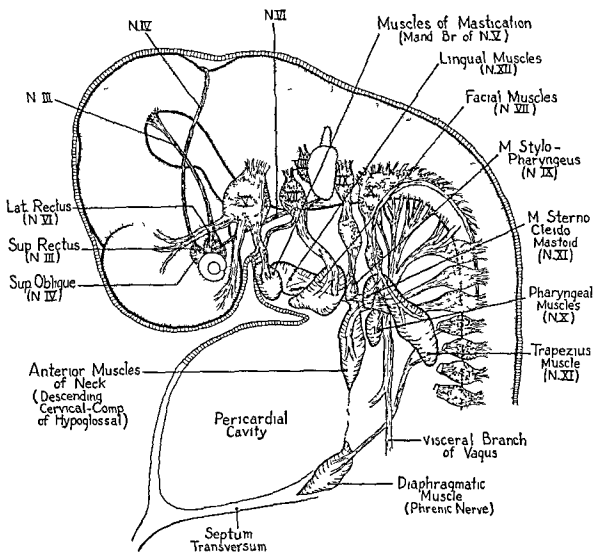


FIG 190 Schematic diagram of 11-mm (sixth week) embryo showing the mesenchymal masses from which the principal groups of cephalic muscles are derived (Modified from W. H. Lewis)

the neck and face arises. Because of this derivation from the mesoderm of the series of gill (branchial) arches, such muscles are described as being of *branchi-omeric origin*. In this part of the body where somites are absent the branchial arches make excellent descriptive landmarks. The statement that a nerve supplies the second branchial arch, or that a muscle arises in the third, has the same exactitude that designation of the somitic level of origin gives in other parts of the body.

From what has been said about the early arrangement of the mesenchyme

As we have already seen, typical mesodermic somites are found throughout the levels that are destined to be incorporated in the neck, and a variable number—usually four—are formed in the occipital part of the head (Fig 182) In the embryos of some of the lower forms there are transitory indications of somites recognizable far forward in the head In the Mammalia, however, with the great specialization of the cephalic region, the limits of such primitive metameres have become largely masked by local specializations and

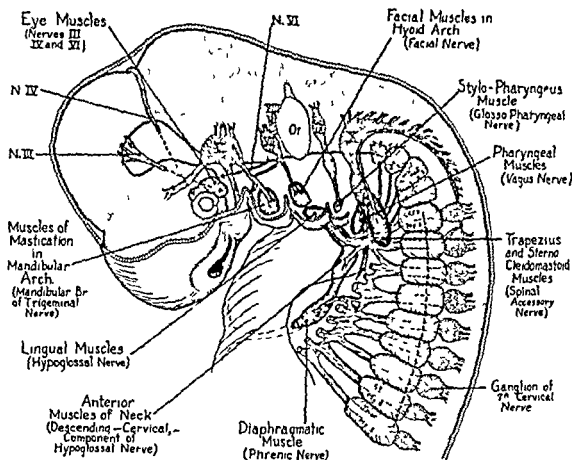


FIG 189 Schematic diagram of 7-mm (five-week) embryo showing the primordial mesenchymal concentrations from which the cephalic muscles are derived (Modified after W H Lewis) Note especially the cranial nerves which are associated with the several premuscle masses and compare this and the following illustrations with Figs 215-217

by secondary fusions Not even in young embryos is it possible to make out any metameric divisions in the mesoderm rostral to the level of the otic vesicles In spite of the absence of any demonstrable segmentation of the preotic mesoderm of mammals in ontogeny, the circumstantial evidence offered by the head somites of primitive forms seems to indicate that the mass of mesoderm from which the *eye muscles* are developed (Figs 189, 190) should be regarded as representing the fusion of persisting parts of about three of the most rostrally located of the head somites of primitive ancestral forms This interpretation is supported by the fact that the innervation of the eye muscles is of the same character as that of muscles of somitic origin in other parts of the body

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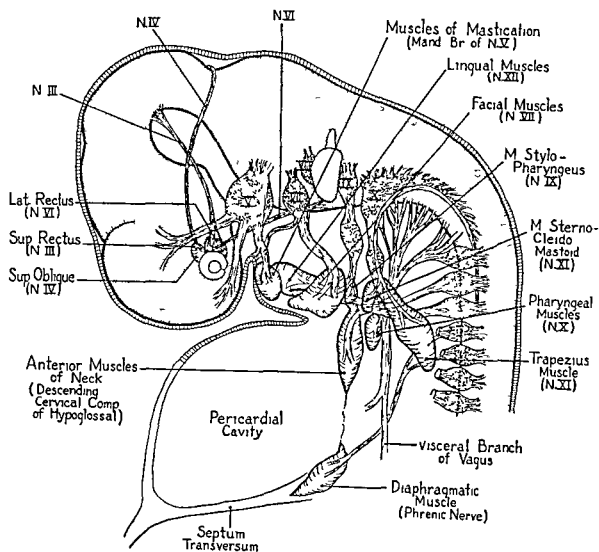


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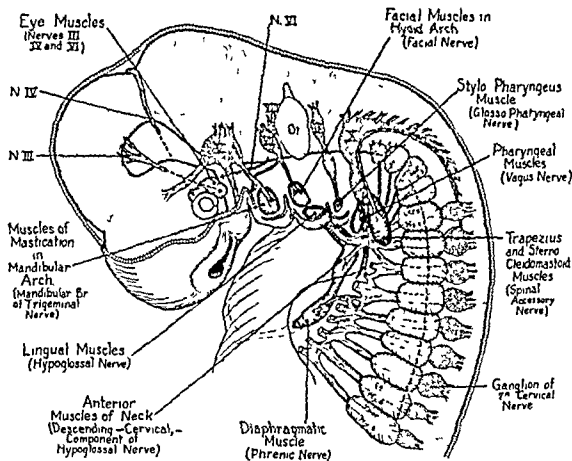


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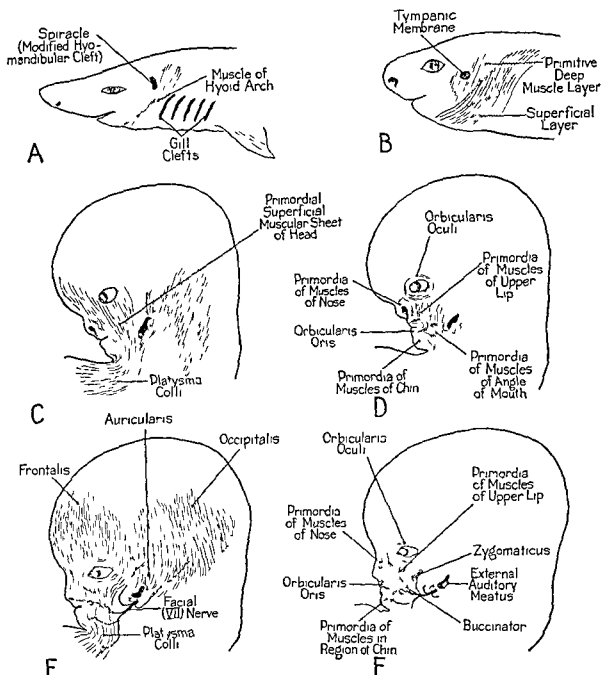


FIG 191 Schematic diagrams indicating the manner in which the muscles of facial expression are derived from the migration and differentiation of hyoid arch muscle A, Location of hyoid arch muscle in shark B, Addition of a superficial sheet of muscle as shown by certain Amphibia (Modified from Ernst Huber) C, Primordial superficial muscle sheet in human embryo of six weeks (After Futamura) D, Deeper primordial muscle layer of six-week embryo becoming organized into muscles about mouth and nose (Modified from Futamura) E, Superficial muscles of head of seven-week embryo (Modified from Futamura) F, Deeper muscles of face in seven week embryo (Modified from Futamura)

in the branchial region it will be readily understood that the primordial masses from which specific muscle groups arise are not at first sharply delimited. It should be realized that Figs. 189 and 190 have been freely schematized to emphasize the relations of these early muscle masses to the branchial arches, and to the cranial nerves with which they are associated. Moreover, it must be borne in mind that the deeper layers of the mesenchyme are involved in the formation of the meningeal covering of the brain, the chondrocranium, and, at later stages, the formation of the membranous bones of the cranium and face, none of which processes are even suggested in these figures drawn particularly to show the muscle primordia.

The primordial mesenchymal mass from which the four recti and two oblique muscles of the eye arise is, from the first, in close relation to the developing optic vesicle (Fig. 189). These muscles are formed by gradual organization in situ, and their adult location (Fig. 193) is not radically different from their point of origin. The relations of the fourth nerve to the superior oblique muscle, of the sixth nerve to the external rectus, and of branches of the third nerve to the remaining eye muscles can be made out as early as the latter part of the second month of development.

In general the muscles of branchiomeristic origin tend to retain the innervation characteristic of the gill-arch stages in phylogeny and ontogeny. Thus we find the muscles which arise from a primordial mesenchymal mass in the mandibular arch (Fig. 189) supplied by motor fibers in the mandibular division of the fifth (trigeminal) nerve (Fig. 219, A). This group includes the *muscles of mastication* (temporal, masseter, and pterygoids) and also the mylohyoid, the anterior belly of the digastric, the tensor veli palatini, the tensor of the Eustachian tube, and the tensor tympani. This utilization of the muscle masses of the mandibular arch region for chewing and swallowing seems quite natural in view of their primary relations.

The *muscles of facial expression* have a much less direct and simple origin. With no muscular tissue between the skin and the bones of the rostral part of the skull, a fish's change of facial expression is limited to the opening and closing of the mouth. Since the muscle arising in the mandibular arch has been pre-empted for chewing and swallowing, the muscles of facial expression must be derived by the migration of other primordial muscle masses into facial territory. With the functional regression of the gills, which occurs with the assumption of air-breathing, the primordial muscle arising in the region of the hyoid arch is the nearest available source. The muscle in this region has started to increase in conspicuousness in Amphibia with the addition of an outer superficial layer which acts as a primitive constrictor of the neck (Fig. 191, B). In the mammals both the deep and the superficial layer of this hyoid arch musculature extend into the facial region. Human embryos of the sixth and seventh weeks show this evolutionary process sketched out in recapitulation. The primordial superficial muscle sheet spreads out onto the front and sides of the head, giving rise to the frontalis, auricularis, and occipitalis muscles (cf Figs. 191, C, E, 192), and to the platysma colli in the cervical region. The

fourth and fifth arches are involved in the formation of the laryngeal cartilages. The primordial muscle masses of the corresponding branchiomic levels give rise to the *muscles of the larynx*, together with the remaining portions of the *pharyngeal constrictors*. As their level of origin would lead one to expect, these muscles are innervated largely by the tenth (vagus) nerve (Figs 193, 216-218)

The *muscles of the tongue* are innervated by the twelfth (hypoglossal) nerve. This nerve represents a fairly recent addition to the cranial group of a nerve

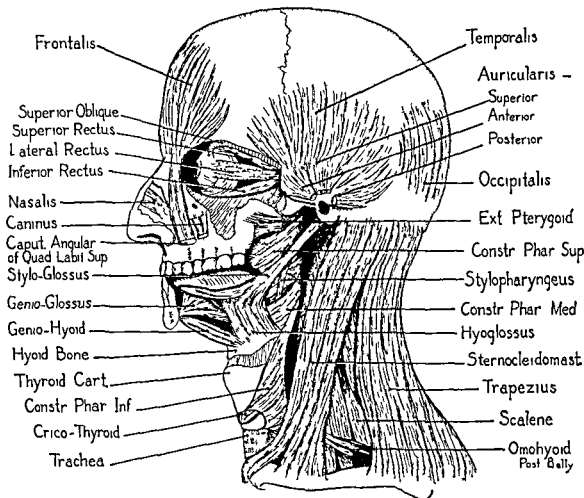


FIG 193 Dissection to show some of the deeper muscles of the adult head and neck (Modified from Corning) The color scheme is the same as in Figs 189, 190, 192

which was phylogenetically spinal. Largely because of their innervation the lingual muscles are thought to be derived from the occipital myotomes. In all probability this interpretation is correct, at least from a phylogenetic standpoint. In mammalian ontogeny, however, the actual migration of pre-muscle elements from these somites into the tongue has yet to be satisfactorily demonstrated.

It has proved difficult, also, to determine the precise origin of the primordial mass of mesoderm supplied by the spinal accessory nerve (XI). This mass first becomes recognizable at such a region that it is hard to be certain whether it is of branchiomic origin or perhaps derived by migration of cells

muscles controlling the movements of the nose and lips are derived largely by subgrouping and rearrangement of the primordial deep layer of muscle from the hyoid arch region (cf Figs 191, D, I, 192, 193). The foregoing brief sketch serves to emphasize the fact that the facial muscles migrate much more extensively during development than is the case with most of the rest of the cephalic musculature. In their migration they carry along with them branches of the seventh nerve and of the external carotid artery which originally furnished the nerve and vascular supply to the hyoid arch. It is only when one

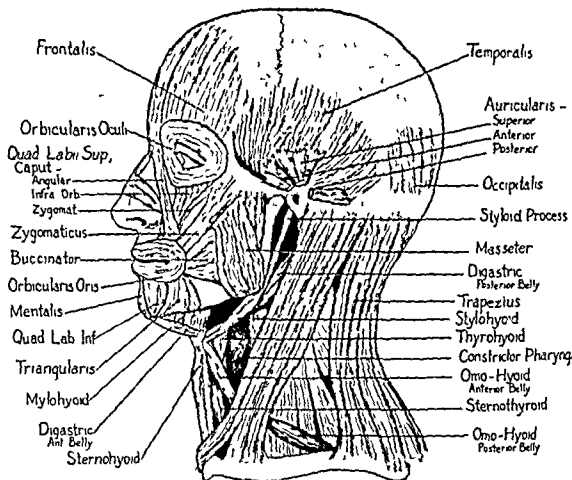


FIG 192 Dissection to show some of the more superficial muscles of the adult head and neck. (Modified from Corning.) The platysma has been removed. The color scheme is the same as that employed in Figs 189 and 190 and indicates the muscles arising in association with the different cranial nerves.

sees the early stages in the development of these muscles that there seems any logic whatever in their arrangement, their innervation, or their blood supply in the adult.

The premuscle masses of the third and fourth branchial arches are smaller than those of the first and second. That in the third arch gives rise to the stylopharyngeus muscle, and to part of the constrictor group of the pharynx. The innervation of these muscles by the ninth (glossopharyngeal) nerve continues to indicate their branchiomeric level of origin after other early landmarks have been obliterated. It will be recalled that the cartilages of the

Development of the Nervous System

FUNCTIONAL SIGNIFICANCE OF THE VARIOUS PARTS OF THE NERVOUS SYSTEM

Without some knowledge of the functional significance of the various parts of the nervous system to serve as a basis for correlation and interpretation, its study from either the developmental or the anatomical point of view is likely to be barren and discouraging. Therefore, even though it involves reviewing some familiar material, and also introducing other material which, conventionally, belongs more in the field of neuroanatomy than in embryology, it seems advisable here to summarize certain conceptions which are essential to an understanding of the activities of the nervous system as a whole and of the rôles played by some of its major divisions. It is hoped that this approach will make the study of the developing nervous system more profitable and more interesting.

Neurons The nervous system is made up of cells which are highly specialized in two of the fundamental properties of protoplasm—irritability and conductivity. These cells develop cytoplasmic processes which extend from one part of the body to another, acting in the manner of telephone lines keeping the various parts of the organism in touch with each other and making possible prompt and co-ordinated responses to alterations in internal or external conditions. In the nervous system of animals as complex as the mammals most lines of communication involve chains of such cells arranged so that the end of the process of one cell comes into close relation with the processes or cell body of another. When a change in environmental conditions (a stimulus) starts a wave of electrochemical change (a nerve impulse) in the protoplasm of one cell in the chain, the wave traverses the processes of the cell in which it was initiated and passes to the next cell in the chain, and so on. Each link in the chain, that is each nerve cell with its processes, is called a *neuron*.

Synapses The point at which the nerve impulse passes from the process of one cell to the processes or the cell body of another is known as a *synapse*. Synapses between neurons appear to be in the nature of "contacts" sufficiently intimate to permit the passage of a nerve impulse, but not ordinarily involving structural continuity of the cell processes. This contact type of relation at a synapse, which is apparently "made" or "broken" under varying physiological conditions, underlies such phenomena as alternative responses to a given stimulus. It implies the possibility of selective routing of the impulse over one

from the occipital somites. Whatever future work may prove to be the situation with regard to this mass from which the *sternocleidomastoid* and *trapezius* muscles are derived, it seems clear that the *infrahyoid* muscles of the front of the neck (Fig. 192, muscles colored yellow) are of somitic origin. These muscles are supplied by the descending cervical branch of the hypoglossal nerve. This branch is composed almost wholly of fibers from the first and second cervical nerves which run for a way with the hypoglossal proper (Fig. 216). Some fibers from the third cervical also join this group more distally.

It is interesting how closely the primordial mass which gives rise to these infrahyoid muscles of the neck is associated with that from which the diaphragmatic musculature arises (Figs. 189, 190). The origin from the fourth and fifth cervical nerves of the phrenic fibers supplying the diaphragm, otherwise so surprising, becomes quite logical in the light of this cervical origin of the primordial mesenchymal mass from which the diaphragmatic muscles are derived.

rons at any or all segmental levels. This arc is involved in the involuntary reaction to a sudden noise.¹

Reflex responses to sudden visual stimulation involve an arc quite similar to that described for reactions initiated by auditory stimuli. The visual arc starts with sensory fibers arising in the retina of the eye. In the superior colliculi, after relay through the thalamus and cortex, the impulses thus initiated discharge over efferent fibers. The efferent fibers communicate with the effector mechanism of the body over paths paralleling those involved in the responses to auditory stimuli. Through this arc would be brought about the automatic recoil from a sudden blinding flash of light.¹

The Cerebellum as a Co-ordinating Center The reflex, whether it is intrasegmental or intersegmental in type, and whether it involves spinal or cranial nerves or centers, constitutes a relatively simple action mechanism. In the complex and more deliberate actions involving several parts of the body and the head, various co-ordinating centers of the brain, such as the cerebellum and the corpus striatum, come into play. The cerebellum receives sensory impulses (position sense) from all segmental levels of the body, and impulses for orientation in space from the semicircular canals and other special neurosensory terminations in the ear. These impulses end in the cerebellum on the same side on which they were initiated.

For example, impulses from a neuromuscular spindle in a voluntary muscle of the neck or arm, or from a Pacinian corpuscle, are transmitted through a peripheral afferent neuron (4a¹) to the spinal cord. This first-order neuron synapses in the dorsal horn of the cervical cord with a second-order afferent neuron (4a²), the process of which crosses to the other side and ascends to the cerebellum. Within the cerebellum it recrosses to the side of the body on which it was initiated. After passing over a series of synapses in the cerebellum (4a³ and 4a⁴), the impulse crosses and may be transmitted (4a⁵) to an efferent center such as the red nucleus (R) in the midbrain. From the red nucleus it again crosses and passes by way of fibers (4e¹) in the rubrospinal tract to the efferent neurons (4e²) of the cervical cord. This neuron chain provides for shifts in position of the head and upper extremity relative to changes in body position in maintaining equilibrium. The various neuron arcs of this type make provision for the maintenance of normal posture, and the tonus of the muscles which makes such posture possible. They make possible smooth, precise, and co-ordinated muscular action, the so-called synergic type of muscular control, of the kind involved in slowly bringing together the tips of the forefingers of the two hands, or touching the forefinger to the tip of nose with the eyes closed. Both of these reactions are commonly used as clinical tests in cases of suspected cerebellar dysfunction.

The physiological interrelation of the vestibular apparatus of the internal

¹ In order to avoid undue complication of the diagram it was expedient to omit the auditory and visual reflex paths from Fig. 194.

of several neuron chains by the occurrence of physiological contact at certain synapses and physiological disjunction at others

The arrangement of neuron chains or arcs, as they are frequently called, is exceedingly complex in the human nervous system. Consideration of its details would carry us far afield, but it is quite possible to have in mind enough of the basic scheme of neuron arrangement so that the various parts of the nervous system assume some meaning in terms of function rather than remaining as mere names, without significance and readily confused.

Functional Classes of Neurons All the myriad neurons which go to make up the central and peripheral nervous system are alike in that they are cells with attenuated processes specialized in conductivity. Among themselves they differ greatly as to location, relations, length, number and distribution of processes, and type and direction of impulses transmitted. Functionally, neurons can be divided into three main groups—afferent, efferent, and association.

AFERENT NEURONS These are of two general orders. First are those that pick up impulses from sensory nerve endings and sense organs (receptors) and carry them into the central nervous system. These first-order afferent neurons constitute one of the characteristic components of the spinal and cranial nerves. Second, there are afferent neurons within the cord and the brain which relay incoming impulses from lower to higher centers.

EFFERENT NEURONS Like the afferent, efferent neurons are of two general categories. First are those which conduct impulses from higher to lower centers within the nervous system. Second, there are those relaying the outgoing impulses from the central nervous system over cranial or spinal nerves to muscles or glands (effectors) which respond by appropriate activity.

ASSOCIATION NEURONS These neurons comprise those neurons and neuron chains which transfer afferent impulses to any one of a number of efferent neuron chains with which their various processes connect.

These three functional categories of neurons—afferent, association, and efferent—together with the receptors attuned to pick up various changes in internal or external conditions, and the effectors capable of carrying out the appropriate responses, constitute what we may call the action system of the organism.

Nerves The various anatomical parts of the nervous system can be translated into terms of afferent, efferent, and association neurons, and studied in the light of their characteristic activities. Thus, what in the dissecting room we call "nerves," are bundles of delicate neuron processes interconnecting various peripherally located structures with the central nervous system. The nuclei and the bulk of the cytoplasm (cell bodies, cytons) of the neurons are either massed at some point on the nerve to form a ganglion, or buried in the cord or brain where they are spoken of as nuclei, or nuclear masses. The nerve itself consists only of the long slender neuron processes (nerve fibers) and the sheaths which protect them.

The Corpus Striatum The corpus striatum, using the term in its most inclusive sense, is a group of nuclear masses differentiated from the deeper portions of the gray matter of the ventrolateral walls of the telencephalon (Fig 204) Functionally, the corpus striatum is concerned in producing smooth, automatic movements where fairly complex motor responses to stimulation are involved From the thalamus—and also from parts of the midbrain—impulses enter the corpus striatum whence, after synapse, they descend over paths to various efferent centers, particularly those of the midbrain (Fig 194, Arc 6) From the midbrain the impulses enter final common paths, such as the rubrospinal tract, along which they proceed, in company with those from cerebellar centers, to efferent neurons of the cord As we have seen by tracing the above arcs, the corpus striatum, like the cerebellum, can be cut into the neuron chains controlling muscular activity When the corpus striatum is thus brought into play, it serves to control the smoothness and steadiness of motor responses and to regulate muscular tonus It is also responsible for the execution of certain so-called automatic associated movements, such as the swaying of the body and the swinging of the arms in walking

Voluntary and Regulatory Control Superimposed on the neuron chains involved in the more stereotyped reactions are mechanisms affording a wide choice of behavior in response to stimuli entering over the various afferent pathways The centers for these highest and most plastic responses are in the cerebral cortex It is perhaps pertinent to emphasize in this connection that in embryological development, as well as in phylogeny, the cerebral cortex is differentiated from the pallial areas of the lateral telencephalic vesicles (Figs 204, 205) Fibers from various receptors enter the cortex by way of the thalamus and are dispersed into localized areas according to their special functions For example, visual impulses initiated by retinal stimulation are carried to the brain by way of the optic nerves In front of the hypophysis, the optic nerves from the two sides intersect to form the optic chiasma where some of the fibers cross to the opposite side and some remain uncrossed (Fig 236) From the chiasma these fibers extend to the visual relay centers (lateral geniculate nuclei) in the thalamus (Fig 194, Arc 5) From the thalamus the impulses are projected to the centers for visual consciousness in the occipital poles of the cerebral hemispheres (Fig 236) The pathways for pain impulses, such as the one indicated from the foot to the cerebral cortex, and for proprioceptive impulses, such as those from the muscles of the neck and arm, have already been discussed and diagrammed (Fig 194) By myriads of association neurons the cortical centers for the reactions specifically mentioned, and for many others, are in free intercommunication Such neurons are responsible for memory and for all choices of action conditioned by previous experience In short, these intercommunicating cortical centers with their appropriate discharge paths provide the basis for intelligent response, in distinction to reflex reactions, to existing conditions Through association neurons of this system, impulses may be transmitted to the efferent neurons

ear and the cerebellum may be illustrated by an experience with which most of us are familiar. When one slips on the ice, the first motor response is a general body reaction in which the arm, leg, trunk, and neck muscles contract in an unco-ordinated manner. The major path involved in this reaction is that already referred to as Arc 3. Traveling this arc, the impulse, which is set off in the semicircular canals when the slipping throws the body out of balance, passes to Deiters' nucleus, whence, after a relay, it proceeds directly through a descending vestibulospinal tract ($3e^1$) to the efferent neurons ($3e^2$) supplying arm, trunk, and leg musculature. At the same time that the vestibular impulse is sent caudalward, it is also projected to the cerebellum ($3'a^1$). From the cerebellum it discharges ($3'e^1$) by way of Deiters' nucleus (D) and the vestibulospinal tract ($3'e^2$) to motor neurons ($3'e^3$). Thus the vestibulospinal tract serves as a final common path, carrying both the impulses shunted directly to the effectors through the vestibular centers of the brain and those relayed over the longer route through the cerebellum. The effect of bringing the cerebellum into play is to make the movements more co-ordinated and so more effective.

From the cerebellum, by way of the midbrain and the thalamus, impulses initiated in the vestibular apparatus are projected forward ($3'a^2$ to $3'a^4$) to the cerebral cortex. This path through the cerebral cortex is, however, relatively long. Consequently, there is an appreciable lapse of time before one is able voluntarily to control his activity through the conscious efferent path (the pyramidal tract, $7e^1$, to the motor centers of the cord supplying arm, trunk, and leg muscles). As a result one usually falls, unless the cerebellar-vestibular reflex responses have proved adequate to meet the situation.

The Thalamus The term thalamus is applied to important aggregations of cell bodies in the lateral walls of the diencephalon (Fig. 205, A). The major portion (dorsal thalamus) serves as a relay center for impulses going to the corpus striatum and to the cerebral cortex. Some examples of afferent pathways passing by way of the thalamus have already been mentioned. It will be recalled that proprioceptive impulses from end-organs of position sense (neuromuscular spindles) or deep pressure sense (Pacinian corpuscles) are projected from the periphery to the thalamus of the opposite side by a two-neuron chain ($4a^1$ and $4'a^2$). Likewise, sensations of pain and temperature, after relay in the cord, cross and are projected to the thalamus. It will be remembered, also, that proprioceptive impulses are routed by way of the cerebellum to the thalamus. These impulses, like the others mentioned, cross to the opposite side of the body from that on which they entered. Specially differentiated portions of the thalamus also receive auditory and visual impulses. These various sensory impulses are projected on the thalamus in characteristic patterns. When these impulses are relayed to the appropriate cortical regions an equally characteristic pattern is there established. Such projection patterns, maintained through different levels, provide the anatomic basis for the so-called localization within the various sensory fields of the cerebral cortex.

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constituting the common motor paths traversing the brain and the spinal cord to any parts of the action system (Arc 7 of Fig. 194 shows the most direct motor path of this type, the pyramidal tract)

SUMMARY

In preparation for considering the development of the nervous system, an attempt has been made to explain some of the fundamental activities carried out in its various parts. By way of summary we may now briefly characterize the major regions in terms of their functions. We should think of the spinal cord and a considerable part of the brain-stem² as having a dual rôle. These parts of the nervous system act as reflex centers and also afford conduction pathways to and from the higher brain centers. The specialized regions developed in the dorsal walls of the mesencephalon (corpora quadrigemina, Fig. 207) are concerned with visual and auditory reflexes. Of these two pairs of local elevations, the more cephalic (superior colliculi) are visual reflex centers, and the more caudal (inferior colliculi) are auditory reflex centers. Functionally, the cerebellum is a center co-ordinating muscular reactions, especially those concerned with the maintenance of normal posture. The dorsal thalamus, situated in the lateral walls of the diencephalon, serves as a gateway for impulses passing to the cerebral cortex. In the deeper part of each cerebral hemisphere is the corpus striatum, which, as we have just seen, is concerned with the regulation of muscle tonus and with the execution of automatic associated movements. The more superficial portions of the cerebral hemispheres become specialized as the cerebral cortex. Certain cortical areas are the highest terminal centers of reception for various types of incoming sensory impulses, such as those resulting from visual, tactile, or proprioceptive stimulation. Other cortical centers contain the cell bodies of neurons which are the first units in efferent chains. Important among such efferent paths are the pyramidal tracts (7c) which place the effector mechanisms of the body under the control of the will. In addition to such afferent and efferent cortical areas, there are large regions interconnected with them which have associative functions. The interplay of these cortical areas permits a choice of response to present stimulation which may be modified by the memory of past experience.

From the standpoint of the experimental biologist, the working out of the neuron arcs which provide the mechanisms controlling different functional activities is a subject of great inherent interest. As our knowledge of this field has grown it has been of increasing importance in clinical medicine. The position of motor and sensory centers, and of the fiber tracts which connect them, are now sufficiently well known so that the location of many brain lesions can be determined accurately by the functions affected. Not all brain lesions, however, make themselves evident by specific motor or sensory disturbances. For example, some recent work seems to indicate that when certain associa-

² Brain stem as usually employed is a convenient term for designating those portions of the brain other than the telencephalon, diencephalon and cerebellum.

tion areas in the frontal lobes of the cerebral hemisphere have their connections with the rest of the brain severed interesting personality changes follow

REVIEW OF EARLY STAGES IN ESTABLISHMENT OF THE NERVOUS SYSTEM

The initial steps in the formation of the nervous system take place very early in development. Directly or indirectly many points of importance in connection with its establishment and early differentiation have already been discussed (See especially the section on the nervous system in Chapter 5). We have considered the origin of the neural groove by the infolding of a thickened plate of ectoderm in the mid-dorsal line of the young embryo, the closure of the neural groove to form the neural tube and the coincident separation of the tube from the parent ectoderm (Figs 48-51, 64).

In the closure of the neural groove, certain cells lying near its margins remain independent, being included neither in the walls of the neural canal nor in the superficial ectoderm as it closes above the newly established neural tube. These ribands of cells come to lie on either side, in the angles between the superficial ectoderm and the neural tube, and constitute the neural crests (Fig 64). They are the primordia of the sensory ganglia of the spinal and the cranial nerves, and indirectly of the sympathetic ganglia.

Almost as soon as it is independently established, the neural tube becomes markedly enlarged cephalically. This dilated anterior portion is the primordium of the brain. Posteriorly the neural tube remains of relatively uniform diameter as the forerunner of the spinal cord.

In its enlargement the brain at first exhibits three regional divisions—the primary forebrain, midbrain, and hindbrain, or, to use their more technical synonyms, the prosencephalon, mesencephalon, and rhombencephalon (Fig 203, A). This three-vesicle stage of the brain is short-lived. The prosencephalon is subdivided into two regions, telencephalon and diencephalon, the mesencephalon remains undivided, and the rhombencephalic region becomes differentiated into metencephalon and myelencephalon. Thus in place of three vesicles, five are established. This stage in the development of the brain is well shown in embryos between 9 and 12 mm in length (Figs 65-68). Starting with these familiar conditions as a basis, we are ready to trace the later differentiation of some of the more important parts of the nervous system.

HISTOGENESIS OF SPINAL CORD AND FORMATION OF SPINAL NERVES

Establishment of Ependymal, Mantle, and Marginal Layers The ectoderm of the open neural groove is at first but a single layer of cells in thickness (Fig 195, A). These original cells proliferate rapidly and, by the time the neural tube has become closed, its wall consists of many cell layers (Fig 195, B). The individual cells, meanwhile, have lost their originally clear-cut outlines and become merged into a syncytium, bounded toward the lumen

constituting the common motor paths traversing the brain and the spinal cord to any parts of the action system (Arc 7 of Fig. 194 shows the most direct motor path of this type, the pyramidal tract)

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* Brain stem as usually employed is a convenient term for designating those portions of the brain other than the telencephalon, diencephalon and cerebellum.

entiation. Its cells continue to divide rapidly and undergo divergent specialization (Fig 196). Some of them become spongioblasts which are destined to form supporting tissue, and some of them differentiate into neuroblasts, which will become functionally active nerve cells. These two types of cells can first be differentiated from each other by the fact that the neuroblasts develop large nuclei whereas the nuclei of the spongioblasts remain somewhat smaller.

Neuroglia The formation of supporting tissue from the spongioblasts involves the development of exceedingly slender and irregular cytoplasmic processes. In association with these processes certain types of neuroglial cells

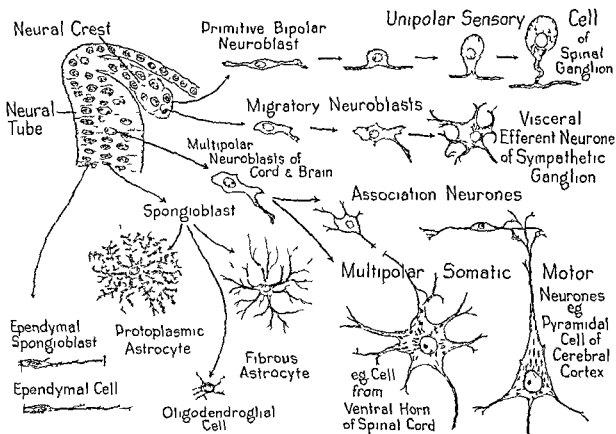


FIG. 196 Schematic diagram illustrating some of the types of nerve cells and neuroglial cells derived from the primitive cells of the neural crest, and the walls of the neural tube

form fibers. Some of these fibers may eventually lose their association with the parent cells but the majority of them retain some connection with the cells from which they were derived. In this respect as well as in its ectodermal origin, neuroglia, as this peculiar connective tissue of the central nervous system is called, differs from the other connective tissues of the body. The fibers and processes formed from the spongioblasts are so delicate that they are exceedingly difficult to demonstrate in material stained by routine histological methods. But when they are subjected to metallic impregnation (e.g., the Golgi silver nitrate method) the glia cell processes and fibers appear as blackened strands forming an elaborate tracery of supporting elements throughout the substance of the central nervous system (Fig 197).

All neuroglial cells exhibit processes of one sort or another and all of them

of the neural tube by an internal limiting membrane, and peripherally by an external limiting membrane (Fig 195, C)

Certain cells lying near the lumen of the neural tube continue conspicuously active in mitosis. They are called germinal cells (Fig 195, C). Most of the new cells formed from the germinal cells are crowded somewhat away from the internal limiting membrane into a zone in the cord which becomes

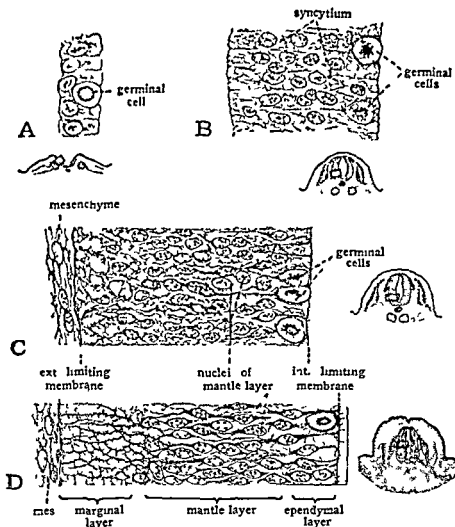


FIG 195 Stages in histogenesis of spinal cord (After Hardesty, Amer Jour Anat, Vol 3, 1904) A, From open neural plate of rabbit embryo B, From wall of recently closed neural tube, 5-mm pig embryo C, From neural tube of 7-mm pig D From neural tube of 10-mm pig (All drawings $\times 550$)

densely packed with nuclei. This zone is called the mantle layer (Fig 195, D). The cells which remain nearest to the internal limiting membrane become more or less elongated and radially arranged about the lumen of the neural tube. They constitute a zone within the mantle layer known as the ependymal layer. Outside the mantle layer is a peripheral region into which practically no nuclei enter. This is the marginal layer (Figs 195, D, 198, A).

Spongioblasts and Neuroblasts Of the three primary layers in the developing spinal cord, the mantle layer is the first to show striking differ-

entiation. Its cells continue to divide rapidly and undergo divergent specialization (Fig 196). Some of them become spongioblasts which are destined to form supporting tissue, and some of them differentiate into neuroblasts, which will become functionally active nerve cells. These two types of cells can first be differentiated from each other by the fact that the neuroblasts develop large nuclei whereas the nuclei of the spongioblasts remain somewhat smaller.

Neuroglia The formation of supporting tissue from the spongioblasts involves the development of exceedingly slender and irregular cytoplasmic processes. In association with these processes certain types of neuroglial cells

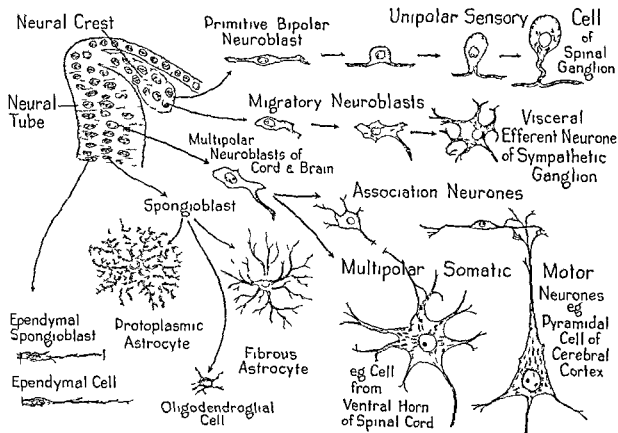


FIG. 196 Schematic diagram illustrating some of the types of nerve cells and neuroglial cells derived from the primitive cells of the neural crest, and the walls of the neural tube

form fibers. Some of these fibers may eventually lose their association with the parent cells but the majority of them retain some connection with the cells from which they were derived. In this respect as well as in its ectodermal origin, neuroglia, as this peculiar connective tissue of the central nervous system is called, differs from the other connective tissues of the body. The fibers and processes formed from the spongioblasts are so delicate that they are exceedingly difficult to demonstrate in material stained by routine histological methods. But when they are subjected to metallic impregnation (e.g., the Golgi silver nitrate method) the 'glia cell processes and fibers appear as blackened strands forming an elaborate tracery of supporting elements throughout the substance of the central nervous system (Fig 197).

All neuroglial cells exhibit processes of one sort or another and all of them

of the neural tube by an internal limiting membrane, and peripherally by an external limiting membrane (Fig 195, C)

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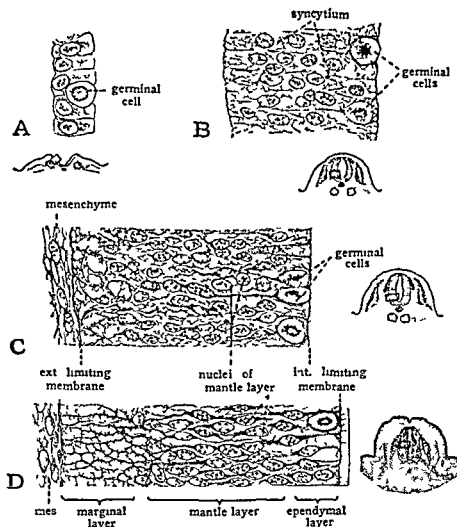


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Spongoblasts and Neuroblasts Of the three primary layers in the developing spinal cord, the mantle layer is the first to show striking differ-

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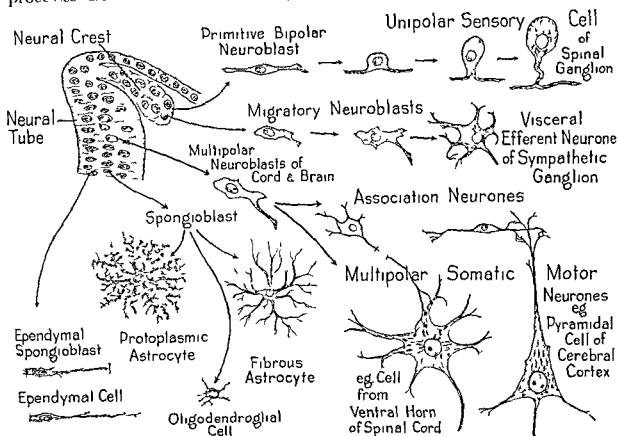


FIG 196 Schematic diagram illustrating some of the types of nerve cells and neuroglial cells derived from the primitive cells of the neural crest, and the walls of the neural tube

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All neuroglial cells exhibit processes of one sort or another and all of them

are supporting in function, but the cells differ much among themselves as to shape and character of processes. For convenience in description they are commonly designated as belonging to one of the following four types: ependymal cells, protoplasmic astrocytes, fibrous astrocytes, oligodendroglial cells.

The *ependymal cells* are the first of the neuroglial elements to differentiate into their characteristic form. They arise from spongioblasts which remain close to the internal limiting membrane but send out long processes all the

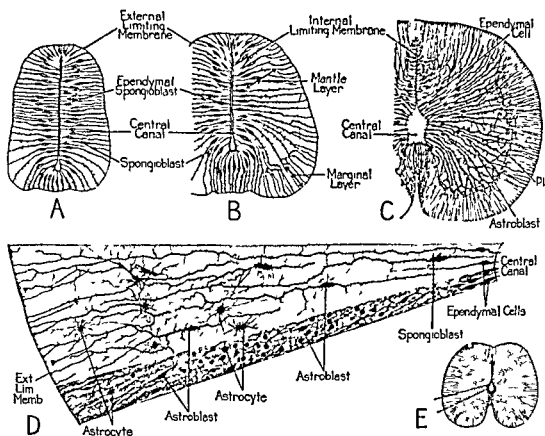


FIG 197 Four stages in development of neuroglia as seen in silver impregnated material which brings out the fibers and slender cell processes (A-C, After Cajal, D, after Hardesty) A, Cord of chick embryo of the third day B, Cord of chick embryo of the fifth day C, Cord of human embryo of 44 mm — note plexiform arrangement of fibers (Pl) at transition from mantle to marginal layer D, Cord of 70-mm pig embryo E, Sketch showing location of section represented in D

way to the external limiting membrane (Fig 197). The end of the ependymal cell which abuts on the central canal becomes ciliated in the embryo. In more advanced fetuses most of the cilia are lost but ciliated patches may occasionally persist in the adult. The peripheral processes of the ependymal cells for the most part lose their connection with the external limiting membrane. The ependymal cells themselves retain their original position bordering the central canal of the cord and the ventricles of the brain.

Both types of astrocytes arise from spongioblasts in the mantle layer and gradually assume the characteristics suggested by their names. They begin to

differentiate somewhat later than the ependymal cells, first becoming recognizable in embryos of about three months (Penfield, 1932) In favorably stained material the fibers in some of the astrocyte processes begin to appear during the fourth month, but neither the fibrous nor the protoplasmic astrocytes have attained their full histological differentiation by the time of birth

The *protoplasmic astrocytes* tend to be located in the gray areas of the central nervous system in association with the cell bodies and dendritic processes of nerve cells

The *fibrous astrocytes* move farther peripherally in the cord and congregate along the developing fiber tracts which constitute the white matter Both types of astrocytes develop platelike terminal enlargements on some of their processes These so-called "terminal feet" become intimately related to the investing membranes of the brain and cord, and participate in the formation of secondary investing membranes about the smaller blood vessels within the substance of the central nervous system The relations of the terminal feet to the meninges are more primitive and appear earlier in development, their relations to blood vessels develop relatively late, not being well established until about the time of birth

Oligodendroglial cells become recognizable developmentally later than the astrocytes, but before the microglia They appear as satellites around the cell bodies of neurons and are scattered along the myelinated nerve tracts of the white matter of the central nervous system Their rapid increase in numbers, beginning in the final months of intra-uterine life and extending through the first year or two after birth, is associated by many observers with the rapid myelination of the fiber tracts of the central nervous system which is occurring at this time

In addition to the four types of neuroglial cells just discussed there is another type of supporting element known as a microglial cell By some workers *microglial cells* are regarded as being of ectodermal origin and consequently as belonging with the other neuroglial types Other authorities believe these cells to be of mesodermal origin and to have wandered into the nervous tissues secondarily from the meninges and from the connective tissue accompanying blood vessels People holding this latter view would group the microglial cells with the ordinary connective tissues rather than with neuroglia Because of this uncertainty as to their origin this cell type was not included in Fig 196 which covers the cells known with certainty to be of ectodermal derivation In development, microglial cells are relatively late in making their appearance They first become recognizable in the last trimester of intra-uterine life through the appearance of an argentophil reaction in their cytoplasm At this stage they are somewhat spindle-shaped Later their characteristics change and they become ameboid and wander throughout the central nervous system When they have arrived at their destination they lose their ameboid proclivities and again change their appearance In this final condition they exhibit branching processes, radiating from a small elongated cell body Under certain pathological conditions they may resume their ameboid

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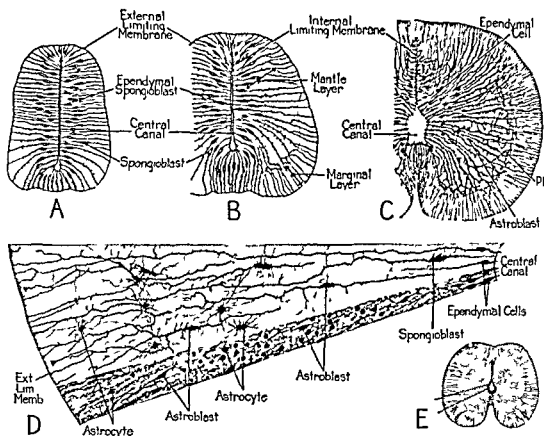


FIG 197 Four stages in development of neuroglia as seen in silver-impregnated material which brings out the fibers and slender cell processes (A-C, After Cyal, D, after Hardesty). A, Cord of chick embryo of the third day. B, Cord of chick embryo of the fifth day. C, Cord of human embryo of 44 mm — note plexiform arrangement of fibers (Pl) at transition from mantle to marginal layer. D, Cord of 70 mm pig embryo. E, Sketch showing location of section represented in D.

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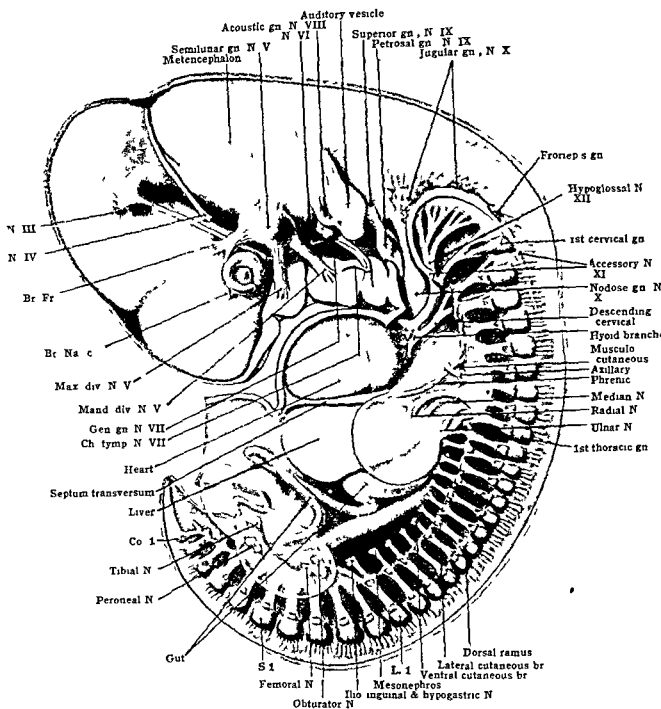


FIG 199 Reconstruction ($\times 15$) of the nervous system of a 10-mm human embryo (After Streeter, *Am J Anat*, Vol 8, 1908)

Abbreviations Br Fr, frontal branch of ophthalmic division of trigeminal nerve, Br Na c, naso-ciliary branch of ophthalmic division of trigeminal nerve, Ch tym p, chorda tympani branch of facial nerve, Co 1, ganglion of first coccygeal nerve, Gn, ganglion, L 1, ganglion of first lumbar nerve, N, nerve, S 1, ganglion of first sacral nerve

shape and activities, at the same time becoming phagocytic and increasing in size

Growth and Migration of Neuroblasts and Formation of Spinal Nerves
Preparations of the spinal cord and dorsal root ganglia made by the routine histological methods do not show the neuroblasts to advantage (Fig 198, A) If, however, a special technic such as intravital staining by methylene blue, or one of the metallic impregnation methods, is used, the slender processes

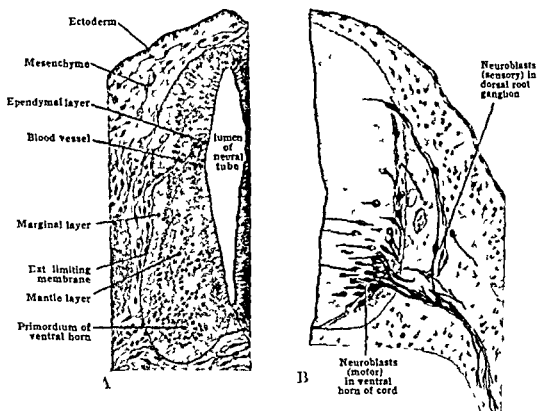


FIG 198 The finer structure of the wall of the neural tube in young embryos A, Neural tube of 9 mm pig embryo, stained with hematoxylin and eosin to show general arrangement of cells at an early stage in differentiation of ependymal, mantle, and marginal layers (After Hardesty) B, Neural tube of a 10 mm pig embryo treated by a silver-impregnation technic to bring out the processes of the developing neuroblasts (After Held) Note manner in which dorsal root of spinal nerve is formed from processes arising from neuroblasts in dorsal ganglion, while ventral root is composed of fibers arising from neuroblasts in the cord

of the neuroblasts can readily be seen (Fig 198, B) With the development of these characteristic nerve fibers we can think of the neuroblasts as having become young neurons

Processes growing out from developing neurons lying in the ventrolateral portions of the mantle layer of the cord establish the *ventral roots* of the spinal nerves (Figs 194, 198, B, 200, 201) Neuroblasts in the dorsal root ganglia send to the cord afferent processes which collectively constitute the *dorsal roots* of the spinal nerves (Fig 198, B) At the same time other processes grow peripherally from the cells of the dorsal root ganglia and ultimately end in

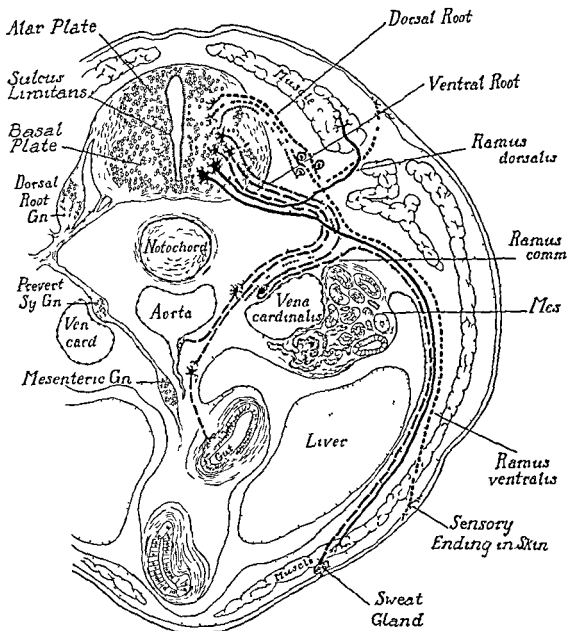


FIG 200 Schematic diagram indicating the various connections made by the neurons which develop in a typical spinal nerve (Modified from Froiep)

Abbreviations Gn ganglion mes mesonephros Prevert Sy Gn prevertebral sympathetic ganglion ramus communis communicans

The neurologist classifies the fibers in a spinal nerve according to their relations and functions. The components of a typical spinal nerve on this basis are

I AFFERENT

A General Somatic Afferent

- (1) Exteroceptive i.e. fibers conducting impulses from the external surface of the body such as touch pain temperature (Represented in Fig 200 by short broken lines)
- (2) Proprioceptive i.e. fibers carrying impulses of position sense from joints tendons and muscles (Represented in Fig 194 4a1)

B General Visceral Afferent

Fibers from viscera (interoceptive) by way of chain ganglion white ramus communicans and dorsal root cell bodies in dorsal root ganglion no synapse before reaching cord (Illustrated in Fig 200 by the dotted line)

II EFFERENT

A General Somatic Efferent

Motor neurons to skeletal muscle cell bodies in ventral columns of gray matter fibers emerge by ventral roots (Illustrated in Fig 200 by solid lines)

B General Visceral Efferent

Two-neuron chains from cord to glands and to smooth muscle of viscera and blood vessels. The first neurons (preganglionic) have their cells of origin in lateral columns of gray matter of cord from first thoracic to third lumbar level. Fibers leave cord by ventral root turn off in white ramus communicans to end in synapse with the second neurons (postganglionic) of the two-neuron chain. Some postganglionic neurons with their cell bodies in chain ganglion send their fibers back by way of a gray ramus communicans into a peripheral nerve to innervate cutaneous glands and blood vessels of the body wall. Other postganglionic neurons with cell bodies either in chain ganglion or collateral ganglia innervate the smooth muscle glands and vessels of the viscera (Three of such two-neuron chains are illustrated in Fig 200 the fibers being shown by interrupted lines)

connection with various types of receptors (Figs 194, 200) These neuroblasts of the dorsal root ganglia are at first bipolar, that is to say they are spindle-shaped with a process arising from either end (Fig 198, B) As they differentiate, the cell body draws to one side and the two processes come off together—in other words, the cell becomes secondarily unipolar (Fig 196)

Neuroblasts which have migrated from the neural crest, and probably also from the spinal cord, form *sympathetic ganglia* The most prominent of such ganglia, often called chain ganglia because of the way they are situated at intervals along the paired prevertebral sympathetic nerve cords, lie on either side of the vertebral column along the dorsal body-wall The neuroblasts of the sympathetic chain ganglia develop into neurons which act as the second elements in two-neuron efferent arcs connecting the spinal cord with involuntary muscle and glands

The first neuron in an arc of this kind is derived from a neuroblast situated in the lateral horn of the gray matter of the cord (Fig 201, D) As the peripheral processes (axons) of such neurons develop, they extend distally by way of the ventral roots of the developing spinal nerves Beyond the point at which the dorsal and the ventral roots join to form the spinal nerve trunk, the processes of such cells turn ventrad to enter the concurrently developing chain ganglion These processes leave the spinal nerves to reach a chain ganglion by way of a branch known as a *ramus communicans* (Fig 200) When these fibers acquire medullary sheaths they become whitish and constitute the *white ramus communicans* of adult terminology Some of the fibers end in a synapse in the ganglion they enter, whereas others pass through this ganglion without synapse and thence along the sympathetic nerve cord to synapse in another ganglion in the chain

From certain neurons in the chain ganglia, fibers turn back in a *ramus communicans* In the adult these recurrent fibers for the most part remain unmyelinated and because of the resultant grayish color of the bundle are said to constitute the *gray ramus communicans* The fibers from the gray ramus enter the peripheral nerve branches and ultimately reach such effectors as sweat glands, the smooth muscle attached to hair follicles, and smooth muscle in the walls of superficial blood vessels (Fig 200)

In addition to the chain ganglia there are other aggregations of sympathetic neurons established by the more extended migration of cells similar to those constituting the chain ganglia Outlying neuron aggregations of this type are known as *collateral ganglia* (e.g., celiac, superior mesenteric) In origin and general course the fibers reaching them from the central nervous system are similar to those going to the chain ganglia If they are destined to reach a collateral ganglion, however, they pass through the chain ganglion without synapse (Fig 200), coming into synaptic relations in the collateral ganglion with the second neuron of the efferent chain

The chain ganglia, the collateral ganglia, and the fibers arising from them constitute the thoracolumbar or *sympathetic division of the autonomic nervous system* The autonomic system has also a *parasympathetic* or *craniosacral division*

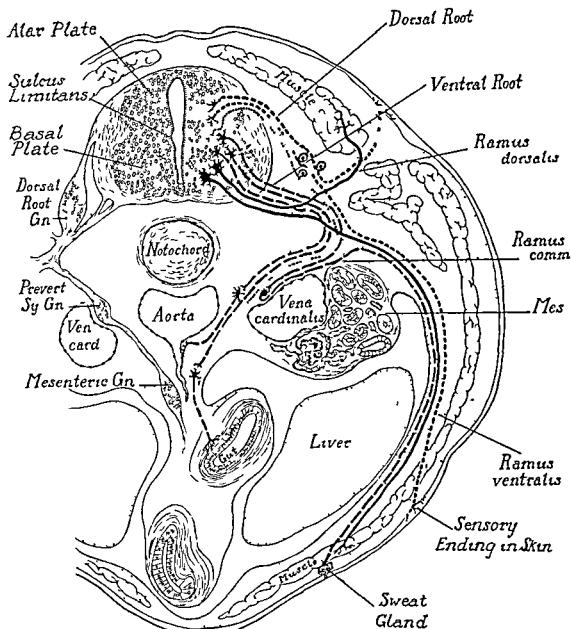


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which can best be discussed after the cranial nerves have been considered. The autonomic system as a whole is concerned with the innervation of involuntary muscle and of glands, both within the body cavities and in the superficial parts of the body.

From the foregoing discussion it is apparent that the typical spinal nerve has in it fibers carrying out a variety of functions. Some of these fibers bring in sensory impulses such as those initiated in the end-organs of pain, touch, and temperature in the body surfaces, and proprioceptive impulses from tendons and from skeletal muscle. These are designated as *general somatic*

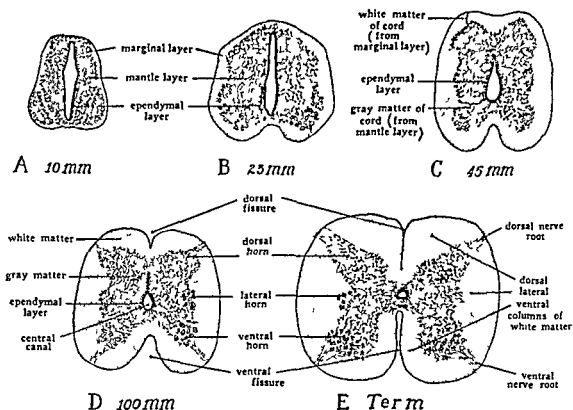


FIG. 201. Transverse sections through spinal cord of pig at various ages. Note especially parts of cord derived from ependymal, mantle, and marginal layers of embryonic neural tube.

afferent fibers. Other afferent neurons (*general visceral afferent*) receive sensory impulses from the viscera. The cell bodies of both somatic and visceral afferent neurons lie in the dorsal root ganglia of spinal nerves. Still other neurons in the spinal nerves are efferent in character. These efferent neurons may be grouped into two categories. One of the categories is made up of neurons having their cell bodies in the ventral horn of the gray matter of the spinal cord and sending their axons to skeletal muscle. These are the *general somatic efferent neurons*. The second category of efferent neurons is composed of the elements of the two-neuron chains to smooth muscle and glands. These are known as *general visceral efferent neurons*. Neuroanatomists speak of such neurons conducting different types of impulses as the *functional components of a spinal nerve*. Fig. 200 illustrates schematically the major components of a typical spinal nerve. In the legend of this figure is a more detailed analysis and

classification of the components which may be studied now by those interested, or may be returned to in connection with the study of neuroanatomy

Formation of Sheaths about Nerve Fibers So far we have discussed only the development and the connections of the neuron processes. As they attain functional maturity many of these processes acquire sheaths that are related to them much as are the insulating sheaths about the wires in a telephone cable. These sheaths fall into two general types, cellular sheaths and myelin sheaths.

The cellular sheaths are somewhat different in the central and in the peripheral nervous systems. In the central nervous system we have seen that one of the types of neuroglia, namely the oligodendroglial cell, was intimately associated with the fibers of nerve tracts. Because of this relationship the oligodendroglial cells are regarded by many workers as constituting a cellular sheath about the fibers which plays a part in their myelination. In the peripheral nerves the cellular sheaths are much more definite. Cells of ectodermal origin migrate along the developing nerve fibers and eventually form a thin cellular investment about them. This sheath is known as the *neurilemma sheath*, or the *gray sheath of Schwann*. All peripheral nerve fibers are inclosed in this neurilemma sheath. In ganglia, both spinal and sympathetic, the neurilemma sheaths investing the neuron processes are continued in the form of cellular sheaths about the cell bodies. Thus, immediately surrounding itself, each ganglion cell has a capsule of so-called satellite cells of ectodermal origin. The ganglion cells and their processes, together with their cellular sheaths, are supported in a framework of typical fibrous connective tissue of mesodermal origin. Peripherally this connective tissue is concentrated to form the capsule of the ganglion. At the points where the nerve bundles enter or leave, the connective tissue constituting the stroma of the ganglion is continuous with the connective-tissue sheaths which surround the nerve fibers and hold them together in the bundles (funiculi) which constitute the nerve trunk.

Another type of investment of nerve fibers is the so-called *myelin sheath*. Fibers covered by this sheath are said to be myelinated, or medullated. They exhibit a glistening white appearance which is imparted to them by the high refractive index of the characteristic fatty substance (myelin) which the sheath contains in abundance. This myelin sheath, if present, is outside the nerve fiber but within the cellular sheath. It should perhaps be emphasized that the formation of a myelin sheath is not peculiar to either the central or the peripheral nervous system. Many fibers in each are medullated, but although they are less conspicuous there are also many nonmedullated fibers both in the peripheral nerve trunks and within the brain and the cord.

The fibers which grow out from the neuroblasts in the dorsal root ganglia and in the cord to establish the peripheral nerves are accompanied by cells of ectodermal origin which migrate along with them. Gradually these accompanying cells spread along the growing nerve fibers and, as we have seen, invest them progressively more completely to form the neurilemma sheath. In the later phases of the acquisition of their cellular sheaths some of the nerve

fibers show indications of the beginning of a myelin sheath. At intervals along the fiber, between it and the sheath cells, small local accumulations of myelin appear. Starting first beneath the sheath cell nucleus, the accumulation of myelin spreads in both directions until it meets a similar accumulation occurring in relation to an adjacent sheath cell. Where these local stretches of myelin formation encounter each other there remains an interruption in the continuity of the sheath known as a node (of Ranvier).

In general, the spread of the process starts near the cell body of a neuron and extends thence peripherally. The process of myelination as described above is based on studies of peripheral nerves. Fibers within the central nervous system lack neurilemma sheaths. Many of them are, nevertheless, myelinated. Although the myelination of such fibers is not so well understood, it seems probable that the oligodendroglial cells play a rôle comparable to that carried out by the neurilemma cells in the myelination of peripheral nerves.

Later Changes in Extent and Relations of Spinal Cord. During the period of development when the neurons are being differentiated and acquiring their sheaths, the spinal cord undergoes marked changes in its relations within the body. In young embryos the neural tube extends the entire length of the body and into the tail (Figs 67, 68). As the spinal column is formed, the growth of the neural arches encloses the spinal cord in the so-called neural canal (Figs 157-159). Up to about three months the neural canal and the spinal cord are co-extensive and the segmentally arranged nerves pass outward through intervertebral spaces directly opposite their point of origin. After this period, differential growth is such that neither the vertebral column nor the neural tube keeps pace with the expansion of the posterior part of the body (Fig 202) and the spinal cord lags much farther behind than does the vertebral column. Since the cephalic part of the central nervous system is firmly fixed within the developing cranium, the effect of this differential growth makes it seem as if the cord were pulled cephalad through the neural canal. Because the nerves are already established before these changes in relations occur, they appear to be dragged out caudally from the cord and to pass back through the neural canal until they arrive at the intervertebral space which was originally opposite their point of origin. Naturally, since it is the cephalic parts of two systems which are fixed with reference to each other, the extent of displacement is progressively greater in the more caudal regions. In a fetus at term the spinal cord ends at about the level of the third lumbar vertebra, except for a small vestigial strand (filum terminale) which represents the regressing terminal portion of the primitive neural tube (Fig 202, D). Postnatally, this differential growth continues until in an adult the end of the cord usually lies near the level of the first lumbar vertebra. Thus the sacral and coccygeal nerves emerging from the cord course almost directly downward for a considerable distance. The group of nerves thus pulled out in the lower portion of the spinal canal constitutes the cauda equina, so called because of its fancied resemblance to a horse's tail.

When it is first formed, the neural tube has a nearly constant diameter except for its terminal taper. Not long after the establishment of the limb buds there are recognizable enlargements of the spinal cord in the segments supplying nerve fibers to the skin and muscles of the growing appendages. These

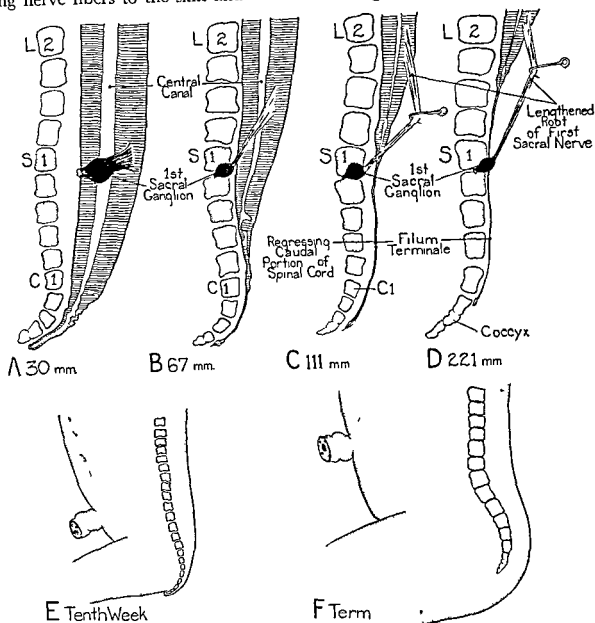


FIG. 202. Diagrams showing changes in relations of caudal end of spinal column and spinal cord due to differential growth. A-D, Relations of the first sacral nerve and ganglion at different ages used as an indicator of the changing position of the spinal cord within the spinal canal (After Streeter, *Am J Anat*, Vol. 25, 1919). E, F, Silhouettes of embryos of (E) ten weeks and (F) at term showing the shift cephalad of caudal part of spinal column (Redrawn, with some modification, after Schultz).

constitute the cervical enlargement of the cord associated with the innervation of the upper extremities, and the lumbosacral enlargement associated with the innervation of the lower extremities.

Development of the Gray and White Matter of the Cord. While these changes in the gross appearance and relations of the cord have been taking place, there have been striking changes in its internal structure. Some of the

fibers show indications of the beginning of a myelin sheath. At intervals along the fiber, between it and the sheath cells, small local accumulations of myelin appear. Starting first beneath the sheath cell nucleus, the accumulation of myelin spreads in both directions until it meets a similar accumulation occurring in relation to an adjacent sheath cell. Where these local stretches of myelin formation encounter each other there remains an interruption in the continuity of the sheath known as a node (of Ranvier).

In general, the spread of the process starts near the cell body of a neuron and extends thence peripherally. The process of myelination as described above is based on studies of peripheral nerves. Fibers within the central nervous system lack neurilemma sheaths. Many of them are, nevertheless, myelinated. Although the myelination of such fibers is not so well understood, it seems probable that the oligodendroglial cells play a rôle comparable to that carried out by the neurilemma cells in the myelination of peripheral nerves.

Later Changes in Extent and Relations of Spinal Cord. During the period of development when the neurons are being differentiated and acquiring their sheaths, the spinal cord undergoes marked changes in its relations within the body. In young embryos the neural tube extends the entire length of the body and into the tail (Figs 67, 68). As the spinal column is formed, the growth of the neural arches encloses the spinal cord in the so-called neural canal (Figs 157-159). Up to about three months the neural canal and the spinal cord are co-extensive and the segmentally arranged nerves pass outward through intervertebral spaces directly opposite their point of origin. After this period, differential growth is such that neither the vertebral column nor the neural tube keeps pace with the expansion of the posterior part of the body (Fig 202) and the spinal cord lags much farther behind than does the vertebral column. Since the cephalic part of the central nervous system is firmly fixed within the developing cranium, the effect of this differential growth makes it seem as if the cord were pulled cephalad through the neural canal. Because the nerves are already established before these changes in relations occur, they appear to be dragged out caudally from the cord and to pass back through the neural canal until they arrive at the intervertebral space which was originally opposite their point of origin. Naturally, since it is the cephalic parts of two systems which are fixed with reference to each other, the extent of displacement is progressively greater in the more caudal regions. In a fetus at term the spinal cord ends at about the level of the third lumbar vertebra, except for a small vestigial strand (filum terminale) which represents the regressing terminal portion of the primitive neural tube (Fig 202, D). Postnatally, this differential growth continues until in an adult the end of the cord usually lies near the level of the first lumbar vertebra. Thus the sacral and coccygeal nerves emerging from the cord course almost directly downward for a considerable distance. The group of nerves thus pulled out in the lower portion of the spinal canal constitutes the cauda equina, so called because of its fancied resemblance to a horse's tail.

nerves and in the ventral commissure of the cord at about the end of the fourth or the beginning of the fifth fetal month. Myelination of the various tracts within the central nervous system tends to follow the sequence in which the tracts developed in phylogeny. Interestingly enough, this same sequence is followed fairly closely by the order in which the various tracts become functionally active in ontogeny. For example, one of the most primitive discharge paths is the vestibulospinal tract. This shows myelination by the sixth fetal month. Another discharge path, less ancient phylogenetically but still premammalian, is the rubrospinal tract which does not show myelination until a month or more later. Finally, there is the corticospinal tract which does not appear in evolution until the mammalian level, and in man's individual development does not begin to myelinate to any extent until after birth. The period of its most rapid myelination (the latter part of the first and the early part of the second postnatal year) is the period in which the infant is acquiring progressively more effective control of its muscular movements culminating in walking.

REGIONAL DIFFERENTIATION OF THE BRAIN

The same five divisions which were established in embryos of six weeks (11-13 mm) remain as the major regions of the adult brain. During their later development they become greatly altered in appearance and certain parts of them receive new names, but their fundamental relations persist. The details of all the structural specializations which appear in the various regions of the brain constitute too complex a story to be handled satisfactorily in brief compass, for any attempt to present them in limited space is almost certain to resolve itself into a mere categorical recital of technical terms which at best is dull, and is all too likely to prove meaningless. Accordingly, we shall confine ourselves to becoming acquainted with the main morphological landmarks and the locations of the principal functional centers of the brain, the bare foundation on which subsequent work may build a fuller knowledge of this interesting system.

THE MYELENCEPHALON

The myelencephalon of the embryo (Fig. 203) becomes the medulla oblongata of the adult brain (Figs. 206-208). Very early in development the lumen of this part of the neural tube becomes dilated, foreshadowing its ultimate fate as the large cavity in the medulla which constitutes the posterior part of the *fourth ventricle* (Fig. 213). At the same time its roof becomes very thin (Fig. 220, C). Small blood vessels develop against this membranous roof and push it ahead of them into the lumen of the fourth ventricle. The freely branching group of vessels thus formed is known as the *posterior choroid plexus*, or the choroid plexus of the fourth ventricle (Figs. 67, 207). This vascular plexus, together with the intimately associated roof of the fourth ventricle which has been thinned so that it consists of only an ependymal layer, constitutes the *tela choroidea*.

neuroblasts in the mantle layer of the cord, as we have seen, send out processes very early in development. Others remain undifferentiated and continue to proliferate for a time, causing continued growth in the mantle layer. As it grows in mass the mantle layer takes on a very characteristic configuration, appearing butterfly-shaped in cross-sections of the cord. With this change in shape, and with the transformation of its spongioblasts into neuroglia and its neuroblasts into characteristic nerve cells, the mantle layer becomes the so-called "*gray matter of the spinal cord*". When characteristically established (Fig. 201, E) the gray matter shows differentiation into dorsal, ventral, and lateral columns. (The columns are often called "horns" because of their configuration in transverse sections, but this designation fails to emphasize their longitudinal continuity.) The dorsal columns are associated with the reception and relaying of afferent impulses, the ventral columns contain the cells of origin for motor fibers to skeletal muscle (Figs. 194, 200). Both of these columns extend throughout the entire length of the cord. In the thoracic and the first three lumbar segments of the cord a lateral column (horn) is also present. This lateral column of gray matter is composed of cells of origin for first elements in two-neuron efferent chains (Fig. 200) supplying smooth muscle and glands. (See also the subsequent section, "Autonomic Nervous System," p. 378.)

During the growth of the mantle layer, the originally extensive lumen of the neural tube is reduced to the small central canal characteristic of the adult cord. By far the greater part of this reduction is effected by the obliteration of what was the dorsal portion of the original lumen (Fig. 201). The cells of the ependymal layer now constitute a sort of epithelioid lining of the central canal.

Meanwhile, the outer or marginal layer of the cord has been increasing extensively in mass. Its growth is due to the secondary addition, outside the gray matter, of longitudinally disposed neuron processes which constitute the conduction paths between the various levels of the spinal cord and the brain (Fig. 194). When, later in development, such fiber tracts become myelinated, they impart to the portions of the cord in which they lie a characteristic whitish appearance contrasting strongly with the gray color of the richly cellular portion of the cord derived from the mantle layer. For this reason the fibers which develop in the marginal layer of the cord are said to constitute its white matter. The main groups of these fibers are more or less marked off from each other by the dorsal and ventral horns of the gray matter. They are known as the dorsal, lateral, and ventral white columns (funiculi) of the cord (Fig. 201). Some of the types of sensory and motor impulses transmitted along the fiber tracts in these white columns have already been discussed in the introductory section of this chapter, and have been schematically diagrammed in Fig. 194.

Age Sequence of Myelination The manner in which myelin is laid down on a nerve fiber has been discussed in a previous section. This process begins at different times in different parts of the nervous system. The earliest myelination is usually recognizable in the dorsal and the ventral roots of the spinal

In dealing with the topography of the walls of the neural tube as they appear in cross-sections, it is customary, in brain levels as well as in the cord, to designate the thickened side-walls as the lateral plates, the thin dorsal wall as the roof plate, and the thin ventral wall as the floor plate. On this basis the membranous covering of the fourth ventricle represents a roof plate greatly stretched out laterally. The process involved is aptly likened by Arey

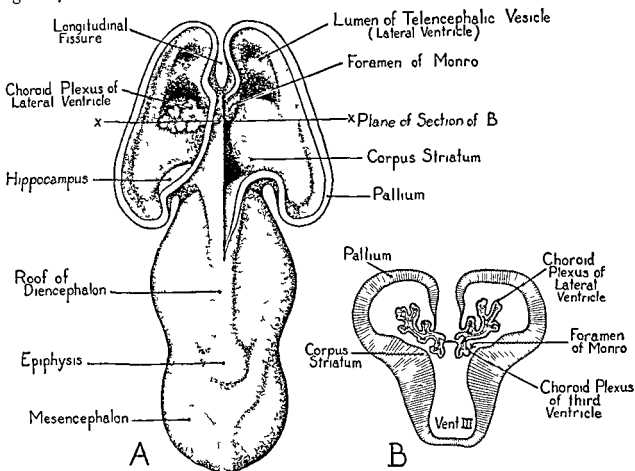


FIG 204 Telencephalon of human embryo during seventh week (After His) A, Viewed from above with parts of the walls removed (As a help in orientation compare the lateral view of a brain of about the same age shown in Fig 203, D) On the left, only the roof of the telencephalic vesicle has been removed to expose the choroid plexus. On the right, the wall of the telencephalic vesicle has been cut away to a deeper level and the choroid plexus of the right lateral ventricle has been removed to show the foramen of Monro. B, Schematic cross section, at the level indicated by the line x—x in A, to show the choroid plexus extending from the roof of the third ventricle through the foramina of Monro into the lateral ventricles.

to opening a book, the hinge of which is represented by the floor plate and the sides of which are represented by the lateral plates of the neural tube (Fig 220). Extending along the inner surface of each lateral plate is a longitudinal sulcus (sulcus limitans) which suggests a division of the lateral plate into a dorsal part (alar plate) and a ventral part (basal plate). The sulcus limitans is clearly marked during the early stages of the development of the myelencephalon. Later it becomes masked in certain regions by the growth of underlying nuclei, but wherever it persists it is a valuable landmark in dealing with

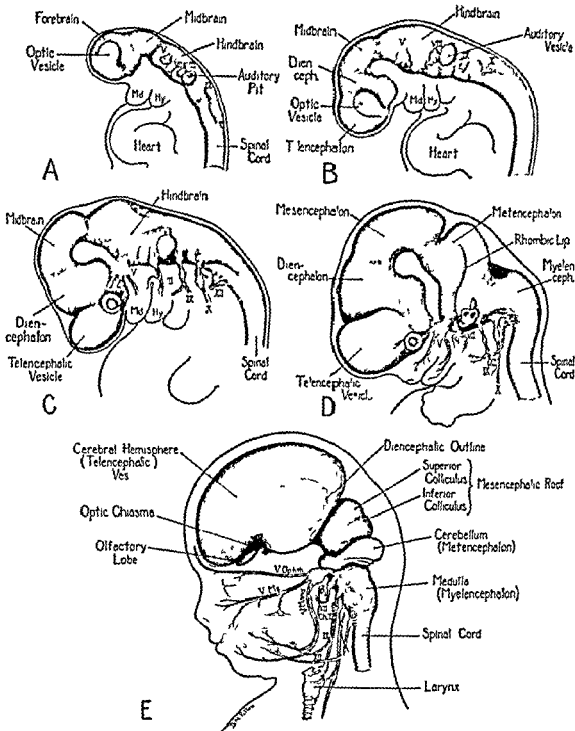


FIG 203 Five stages in early development of brain and cranial nerves (Adapted from various sources, primarily figures by Streeter and reconstructions in the Carnegie Collection) A, At 20 somites—based on the Davis embryo—probable fertilization age of three and a half weeks B, At 4 mm, fertilization age of about four weeks C, At 8 mm, fertilization age of about five and a third weeks D, At 17 mm, fertilization age of about seven weeks E, At 50 to 60 mm, fertilization age of about 11 weeks The cranial nerves shown are indicated by the appropriate Roman numerals V, trigeminal, VII, facial, VIII, acoustic, IX, glossopharyngeal, X, vagus, XI, accessory, XII, hypoglossal
Abbreviations Ch T, Chorda tympani branch of seventh nerve, Hy, hyoid arch, Md, mandibular arch V Mand, mandibular branch of trigeminal nerve, V Max, maxillary branch, V Ophth, ophthalmic branch

the location of the nuclei and the fiber tracts. In the brain, as in the cord, afferent centers develop dorsal, and efferent centers ventral to the sulcus limitans.

Especially in very early stages of development the myelencephalon shows, in the form of internuromeric constrictions, unmistakable evidences of its fundamental segmental character. These constrictions are most conspicuous in parasagittal sections of embryos toward the close of the first, and in the early part of the second month of development. Their significance in phylogeny was mentioned in Chapter 5, their relations to the cranial nerve nuclei will be discussed in the section on the cranial nerves in the latter part of this chapter.

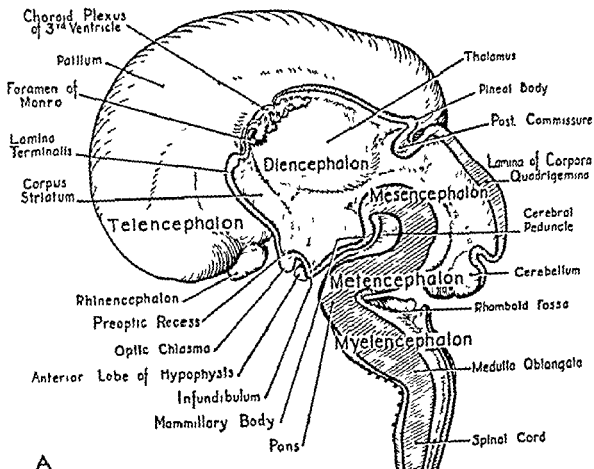
The walls of the neural tube in the brain region show the same early histological changes which occur in the walls of the spinal cord, with the resulting establishment of ependymal, mantle, and marginal layers. The ependymal layer of the myelencephalon becomes the epithelioid lining of the fourth ventricle. The manner in which the tectal portion of the ependyma becomes associated with the choroid plexus has already been pointed out.

In dealing with the spinal cord we traced the way in which the mantle layer gave rise to the columns of its gray matter. In the myelencephalon the mantle layer starts to differentiate in similar fashion, but local specializations modify the pattern and interrupt to some extent the continuity of the columns. When, in the course of such modification, a portion of the gray matter has become more or less circumscribed, it is called a nucleus. Except for noting their derivation from the mantle layer, the myelencephalic nuclei can most profitably be considered later, in connection with the cranial nerves.

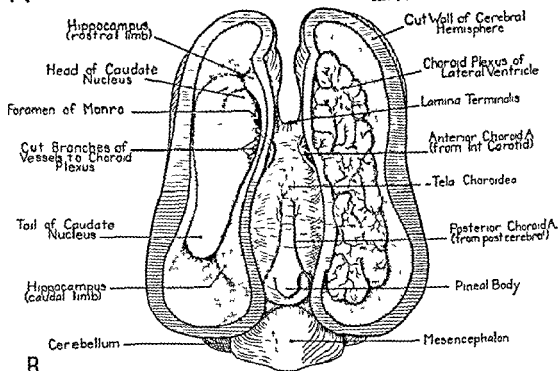
Concurrently with the differentiation of the nuclear (gray) masses, the marginal layer also becomes specialized. In this process, there is first the ingrowth of longitudinally disposed fiber tracts constituting the conduction pathways interconnecting the spinal cord and the brain (Fig. 194). Eventually most of these tracts become myelinated, thus establishing characteristic white matter similar to that in the cord. In the myelencephalon, however, the growth and secondary migration of certain nuclear groups produce a considerable intermingling of gray and white which stands in contrast with the sharply marked off peripheral white matter of the cord.

THE METENCEPHALON

From the standpoint of phylogeny and ontogeny, the metencephalon may be regarded as composed of three parts. The primary portion is the forward continuation of the medulla which in young embryos was the cephalic part of the old rhombencephalon. This part eventually constitutes the axial portion of the metencephalon (the so-called tegmentum of the pons) in the adult brain. Developing from the dorsolateral portions of the rhombencephalon at this level is a second part of the metencephalon which is small and inconspicuous in the lowest vertebrates. This region is the cerebellum, which becomes enlarged and specialized in forms exhibiting complex and highly coordinated muscular movements. It reaches the peak of its development only



A



B

FIG 205 Diagrams showing general structure of brain in an embryo of three months (Modified from His) A, Sagittal section, with right hemisphere shown in perspective B, Cerebral hemispheres opened from above, on right, choroid plexus of lateral ventricle is represented in situ, on left, choroid plexus has been removed to expose hippocampus and caudate nucleus

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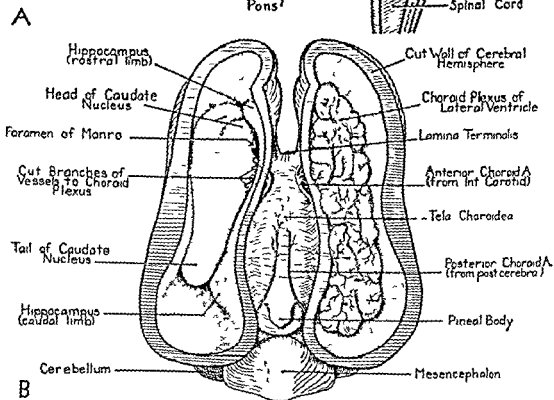
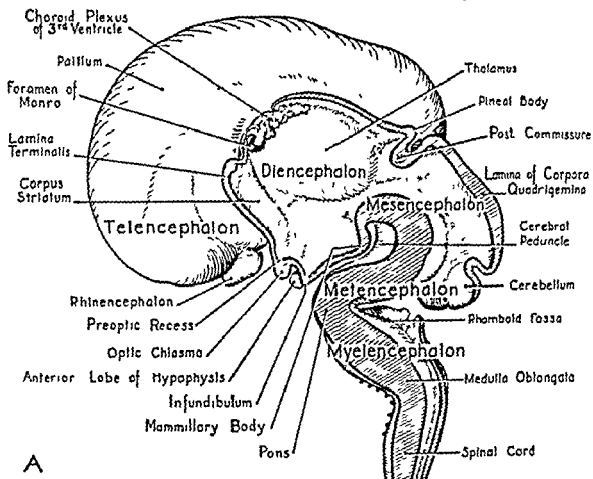


FIG. 205 Diagrams showing general structure of brain in an embryo of three months (Modified from His) A, Sagittal section, with right hemisphere shown in perspective B, Cerebral hemispheres opened from above, on right, choroid plexus of lateral ventricle is represented in situ, on left, choroid plexus has been removed to expose hippocampus and caudate nucleus

Some of the more important nuclei of this region will be considered in the section on cranial nerves. The same longitudinal fiber tracts which, on their way to and from higher centers in the brain, traversed the marginal layer of the medulla are continued in comparable positions through the axial portion of the metencephalon (Fig 194). These tracts are supplemented by the addition of other fiber bundles which arise in the medulla and pons.

The Cerebellum In order to understand the origin of the cerebellum it is necessary to have clearly in mind certain features of the early topography of the rhombencephalon. The manner in which the lateral walls of the rhombencephalon spread apart with the resultant stretching out of the roof plate has already been discussed in connection with the formation of the choroid plexus of the fourth ventricle. The zone of abrupt thickening on either side where there is a transition from the thin roof to the thick lateral plates is known as the rhombic lip (Fig 203, D). In older embryos the rhombic lip is flange-shaped, as seen in cross-sections (Fig 220, E). If this part of the brain is viewed from above, the rhombic lips will be seen flanking the developing fourth ventricle. In young embryos the fourth ventricle is a rather elongated space (Fig 213, B, C). When, during the second month, a sharp flexure develops in the future pontine region, the rhombic lips are squeezed together cephalocaudally and as a result bulge out to either side (Cf C and D, Fig 203). The outward extensions of the rhombocoele between these lips are known as the lateral recesses of the fourth ventricle (Fig 209, B). The part of the rhombic lip which is situated cephalic to the lateral recess grows to form the flocculo-nodular lobe of the cerebellum (Fig 209, C-F). We shall see, when the central connections of the vestibular apparatus are discussed, that their associated nuclei differentiate in large part in that portion of the rhombic lip just caudal to the lateral recess. Consequently these centers develop in close proximity to the flocculo-nodular lobe with which they become intimately interconnected to establish this portion of the brain as a major center for equilibratory control. Phylogenetically, this flocculo-nodular lobe of the cerebellum dates back to the beginning of the vertebrate series. It is interesting in this connection to see its early establishment in human ontogeny.

Cephalic to the part of the cerebellum developing from the rhombic lip is the so-called corpus cerebelli. This term is used to include all the developing cerebellum except the flocculo-nodular lobe from which it is separated by the posterolateral fissure (Fig 209, A, B). The corpus cerebelli is formed by growth of the alar plates where they swing toward the mid-line rostral to the lateral recesses of the fourth ventricle. The first expansion of this region takes place toward the fourth ventricle (second month), but soon thereafter (third month) the growth becomes evident externally (Fig 209, B). From the manner in which this region is molded in the formation of the pontine flexure, it is evident that the cerebellar primordia are paired structures arising from limited parts of the right and left alar plates. These two centers of growth soon coalesce in the mid-line. Their more medial portions grow together to

in primates. The co-ordinating function of this part of the brain has already been explained in the introductory section of this chapter, and some of the types of fiber paths leading to and from it were there shown diagrammatically (Fig. 194). The third part of the metencephalon is the portion usually called the basal or fibrous part of the pons.

Primary Axial Portion of the Metencephalon Unfortunately, the portion of the metencephalon embraced by the fibrous portion of the pons has been included by descriptive anatomists as a part of the mammalian pons, constituting the so-called tegmentum. This inclusion of the primitive axial

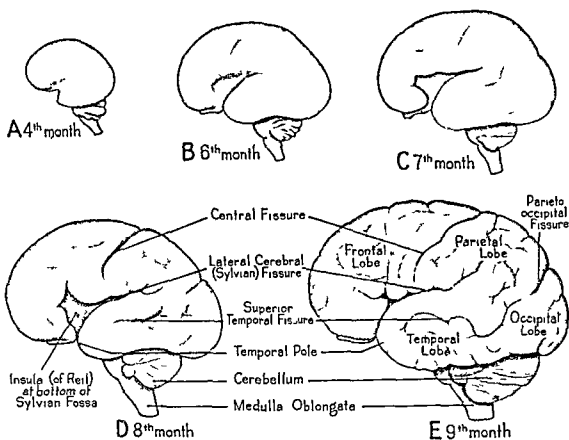


FIG. 206 Lateral views of fetal brain at various stages in development (Modified from Retzius)

portion of the metencephalon in the designation "pons" is justified neither by its functional character, nor by its developmental history. The primary axial portion of the metencephalon (BNA, *tegmentum pontis*), as would be expected from the fact that it is a continuation of the medulla, exhibits a similar organization. The alar and basal plates are similarly disposed dorsal to, and ventral to, the sulcus limitans. As was noted in connection with the medulla, the sulcus limitans is clearly marked in the embryo. In certain regions it still remains as a recognizable landmark in the adult, although it becomes partially obscured locally as a result of secondary changes in the position of nuclei and fiber tracts. As was the case both in the cord and the medulla, afferent nuclei are located dorsal to the sulcus limitans and efferent nuclei ventral to it.

Some of the more important nuclei of this region will be considered in the section on cranial nerves. The same longitudinal fiber tracts which, on their way to and from higher centers in the brain, traversed the marginal layer of the medulla are continued in comparable positions through the axial portion of the metencephalon (Fig 194). These tracts are supplemented by the addition of other fiber bundles which arise in the medulla and pons.

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form the vermis. On either side of the vermis there is rapid expansion resulting in the formation of the cerebellar hemispheres (Fig. 209, D).

During the fourth and fifth months there is particularly rapid growth of the superficial parts of the cerebellum. This results in the development of numerous lobules and fissures. Here we need consider only certain fundamental

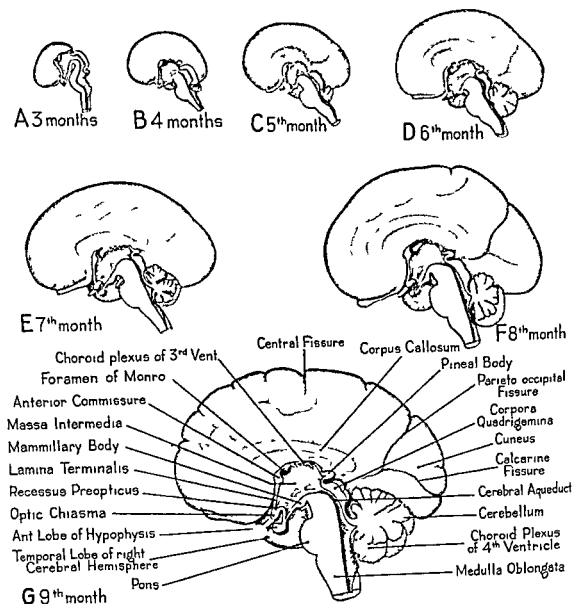


FIG. 207. Sagittal sections of fetal brain at various stages of development (Modified from Retzius.)

subdivisions thus formed. We have already seen how the flocculo-nodular lobe was marked off from the corpus cerebelli by the posterolateral fissure. During the fourth month the so-called fissura prima appears, subdividing the corpus cerebelli transversely. We then have established the three fundamental regions of the cerebellum called (Larsell-Dow terminology) the anterior, the posterior, and the flocculo-nodular lobes. From the fifth to the seventh month local areas become specialized within these primary lobes. Some of these

which are of particular interest in neuroanatomy have been labeled in Fig 209 for future reference. It would carry us beyond the scope of this book to discuss here either the details of the differentiation of these areas or the associated histological changes.

Basal Portion of the Pons The fibrous or basal portion of the pons appears in evolution only with the mammals. It is intimately related structurally and functionally to the cerebellar hemispheres and like these structures reaches the height of its development only in primates. It is composed essentially of

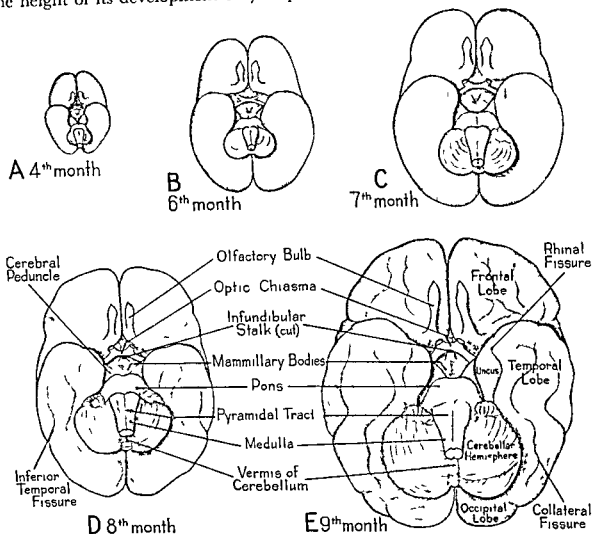


FIG 208 Ventral views of fetal brains at various stages of development (Modified from Retzius)

fiber tracts leading to the cerebellar hemispheres, although there is some intermingling of gray matter, and some through fiber tracts traverse it. As one might deduce from its late appearance in phylogeny, the fibrous portion of the pons is laid down secondarily in the ventrolateral margins of the original rhombencephalon. Although its location is early indicated in embryos by the pontine flexure, its fiber paths are relatively late in making their appearance.

THE MESENCEPHALON

The mesencephalon consists of three major regions—the tectum, a middle portion (tegmentum), and the peduncular portion.

Tectum of the Mesencephalon The tectum arises from the dorsolateral walls of the mesencephalon and is made up of two pairs of eminences, known as the superior and the inferior colliculi. These four elevations are often called the corpora quadrigemina. Sometimes the superior colliculi are termed the anterior, and the inferior colliculi the posterior quadrigeminal bodies. It

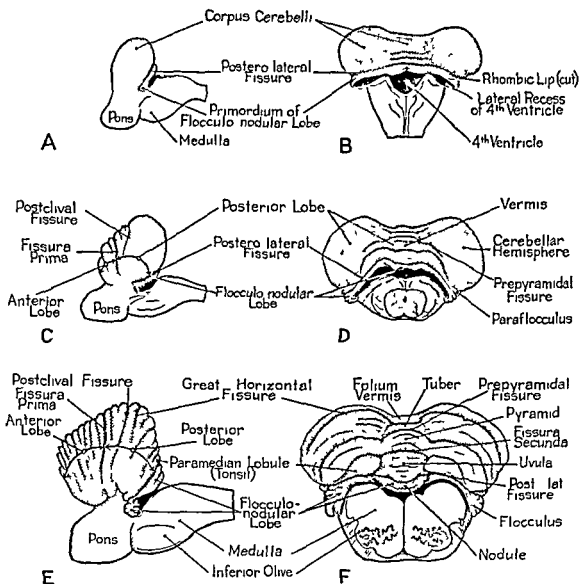


FIG 209 Three stages in development of cerebellum (Modified from Streeter) A, Lateral, and B, dorsal view of a reconstruction from an embryo of 95 mm (13 weeks) C, Lateral, and D, dorsal view of reconstruction from an embryo of four months E, Lateral, and F, dorsal view of reconstruction of an embryo of five months Labeling follows Larsell-Dow terminology

will be recalled that the inferior colliculi serve as synaptic relay stations for auditory reflexes, and that the superior colliculi are visual correlation and reflex centers

Although they develop in close association, the superior and inferior colliculi exhibit interesting differences in their manner of growth, and their final structural patterns. The inferior colliculi show a relatively simple type of

differentiation, being developed primarily as enlarged gray areas arising from the alar plate portion of the mantle layer of the young brain, and retaining their original relations with little secondary modification. In contrast, the superior colliculi, which start to develop in the same manner, undergo striking modifications of the original pattern. A large proportion of the neuroblasts derived from the mantle layer migrate toward the surface and acquire a conspicuously stratified arrangement. Between these layers of cells run incoming fiber bundles. The outgoing fibers lie deep to these migrated bands of cells and the incoming fibers associated with them. This elaborate laminated arrangement of cells and fibers is indicative of the correlative function of this part of the tectum. It is here that visual psychic impulses are correlated with pain and temperature impulses from the head and body with the resultant initiation of the appropriate responses. Auditory impulses are also passed on from the inferior to the superior colliculi providing for auditory-visual correlation. It is in this region, too, that these various impulses may be modified or conditioned through connections from the cerebral cortex.

Middle Portion of the Mesencephalon The middle portion of the mesencephalon, frequently called the *tegmentum*,³ is developed from the basal plates of the embryonic neural tube at this level. It contains the nuclei of origin of the third (oculomotor) nerves at the level of the superior colliculi, and of the fourth (trochlear) nerves at the level of the inferior colliculi. The relations of these nuclei will receive further consideration in a following section on the cranial nerves. Other conspicuous and important gray masses in the tegmentum of the mesencephalon are the *red nuclei*. These nuclei are located on either side, close to the mid-line. Each nucleus consists of a large-celled and a small-celled portion. The large-celled moiety acts as a relay station for impulses passing from the cerebellum to the motor centers of the brain-stem and the cervical cord (Fig. 194). The small-celled part which appears later in both phylogeny and ontogeny, serves as a relay station for impulses passing from the cerebellum to higher centers. In addition to the nuclear masses mentioned, and others of somewhat similar significance, there are many fiber tracts in the tegmentum. A considerable proportion of these tracts are "fibers of passage," that is to say they are fibers carrying impulses which have originated, and are destined to terminate, at other levels.

Peduncular Region The peduncular region consists primarily of longitudinal fiber tracts which develop in the marginal layer of the basal portions of the mesencephalon. Lying dorsally along these fiber tracts is a mass of gray matter known as the *substantia nigra* which is also regarded as part of the peduncular region. This nuclear mass gets its name from the fact that it contains a black pigment (melanin). This pigment is relatively late in appearing, there being only scanty amounts of it present at the time of birth. Its most

³ The word *tegmentum* means a covering. It was originally applied to the dorsal part of the pons before it was realized that the thin choroid layer was the true roof of this region of the brain. The forward continuation of this zone into the mesencephalon later received the same unfortunate appellation.

rapid increase commences around the sixth or seventh year and continues into adolescence

The fiber tracts of the peduncular region (*crura cerebri*), being for the most part descending paths from the cerebral cortex (e g, pyramidal tract, Fig 194, 7c), are relatively late in developing in ontogeny, as in phylogeny. As a matter of fact, it is not until after birth that these tracts become medullated. Consequently, the peduncular part of the midbrain in the embryo lacks two of its most striking adult characteristics, the abundant melanin pigment of the substantia nigra, and the heavy medullation of the fiber tracts of the *crura cerebri*.

The Mesocoele With the great thickening of its walls, the lumen of the mesencephalon becomes relatively reduced to form a narrow canal joining the lumen of the metencephalon and myelencephalon (fourth ventricle) with the lumen of the diencephalon (third ventricle). This canal is known as the *cerebral aqueduct* or *aqueduct of Sylvius* (Fig 213).

THE DIENCEPHALON

Although the diencephalon undergoes striking local modifications, its original name is still retained in the terminology of adult anatomy. Three subdivisions are customarily recognized in this part of the brain—the epithalamus, the thalamus, and the hypothalamus.

The Epithalamus The epithalamus is formed from the embryonic roof plate and the more dorsal portions of the alar plates. During the second month the thin roof plate expands. Vessels developing on its outer surface force it ahead of them in fingerlike processes which, early in the third month, begin to project into the diocoele. The attenuated roof plate, together with the associated capillaries, constitutes a choroid plexus (*choroid plexus of the third ventricle*, Figs 205, A, 207, G). In the median part of the diencephalic roof, posterior to the choroid plexus, the *epiphysis* (pineal body) appears during the seventh week as a small local evagination (Figs 205, A, 207). Later in development the walls of the epiphysis become thickened, and its lumen is practically obliterated.

In addition to the choroid plexus and the epiphysis, which are essentially non-nervous derivatives of the roof plate, there are nuclear masses and fiber tracts which arise along the upper borders of the alar plates. The nuclear masses are the paired *habenulae*, interconnected by a commissure which crosses the mid-line just rostral to the epiphysis. According to Streeter, these nuclei can be clearly outlined and some of their connections discerned in embryos of 80 mm (thirteenth week). The *habenular complex* is one of the links in the chain of central olfactory conduction paths. Just caudal to the epiphysis at the transition from diencephalon to mesencephalon another band of crossing fibers develops which is known as the posterior commissure.

The Thalamus The thalamus is a group of nuclear masses developing in the lateral walls of the diencephalon. It may be subdivided into a dorsal

thalamus and a ventral thalamus or subthalamus. On the lateral walls of the ventricles a sulcus (sulcus hypothalamicus—shown below the word *diencephalon* but not labeled in Fig 205, A) indicates the ventral border of the dorsal thalamus. The main portion of the sulcus hypothalamicus is regarded by some observers as the prolongation of the sulcus limitans into this part of the brain. The rostral bifurcation of the sulcus, however, has left the anterior termination of the sulcus limitans a matter of controversy.

DORSAL THALAMUS This contains nuclear groups which are way stations for various types of afferent impulses en route to the cerebral cortex. One group (*ventral nucleus of dorsal thalamus*) is a conscious and a relay center for proprioceptive, tactile, pain, and temperature impulses (Fig 194). Another conspicuous nuclear group (*lateral geniculate nucleus*) receives visual impulses and transmits them to the visual centers of the cerebral cortex (Figs 194, 236). Still another nuclear mass (*medial geniculate nucleus*) is the thalamic region for the reception and transmission of auditory impulses to the cerebral cortex. There are other centers in the dorsal thalamus in addition to those named, the examples cited will, however, serve to indicate the general functional character of this portion of the diencephalon. According to Streeter, it begins to be possible to recognize the major pathways entering and leaving the thalamus by the end of the second month. By the end of the third month the thalamic centers have enlarged sufficiently to cause a conspicuous bulge on the medial surfaces of the diencephalic walls (Fig 205, A).

The thickening of the lateral walls of the diencephalon greatly reduces the width of its lumen. In its central portion the two walls may come in contact and fuse, forming a conspicuous connection across the third ventricle, known as the *massa intermedia*. If it is formed, this fusion involves the gray matter of the dorsal thalamus.

VENTRAL THALAMUS This is a region of passage, and to some extent of relay, of fiber tracts from the deeper portions of the hemispheres to efferent centers. It grades over into the tegmentum of the midbrain.

The Hypothalamus The hypothalamus develops from the basal plates and the floor plate of the diencephalon. Intimately associated with it is a gland of internal secretion, the *hypophysis*, the neural lobe of which is derived from the diencephalic floor plate. (See Chapter 17 on the ductless glands.) In the floor, as in the roof, of the diencephalon conspicuous groups of fibers cross the mid-line. The most significant of these is in the *optic chiasma* where part of the entering optic nerve fibers decussate to continue—in company with uncrossed fibers—as the optic tracts (Fig 236). It will be recalled that very early in development the optic vesicles arise as outgrowths from the ventrolateral walls of the prosencephalon (Fig 203, A, B). When the prosencephalon is divided into telencephalon and diencephalon, the optic stalks open into the brain very near the new boundary. In fact, the median depression in the floor of the brain, opposite their point of entrance, is regarded as the ventral landmark (*recessus opticus*, Fig 67) which establishes the line of demarcation between telencephalon and diencephalon. The chiasmal thickening makes its

appearance directly caudal to the recessus opticus. It is usually recognizable in human embryos of the fifth week, and clearly defined by the sixth week.

The mantle layer of the hypothalamic portion of the diencephalon differentiates into a series of nuclei. Conspicuous among these are the paired *mammillary bodies* which appear relatively early in development and form rounded protuberances on the ventral surface of the caudal part of the hypothalamus (Figs 207, 208). The hypothalamic nuclei act as olfacto-visceral centers where olfactory impulses are correlated with visceral impulses such as those of taste. Perhaps more significantly, in primates, this region has certain nuclei exercising a regulatory action over parasympathetic centers of the brain-stem, and other nuclei with a similar relation to the sympathetic centers of the spinal cord. Thus the region as a whole is concerned with the regulation of visceral functions such as maintenance of normal heart rate, and of normal body temperature, and effective muscular action of the internal organs generally.

THE TELLENCEPHALON

The telencephalon consists of the most anterior part of the neural tube, including paired dorsolateral outgrowths from its primary median portion. These outgrowths first appear as roughly hemispherical evaginations called the *telencephalic vesicles* (Fig 203). Although the division of the lateral walls of the neural tube into alar and basal plates is not clearly marked in this region, the telencephalic evaginations, because of their general relations, are regarded as arising chiefly from the alar plates.

At first the cavities within the two telencephalic vesicles are broadly continuous with the primary lumen of the neural tube (Figs 204, B, 213, B). Later in development these openings into the lateral vesicles become relatively much smaller, nevertheless they persist, even in the adult, as the so-called *foramina of Monro or interventricular foramina* (Fig 213). Thus, in spite of extensive local modifications, the original neural canal remains open. In the adult brain the lateral telocoeles are known as the first and second ventricles. Since there is no line of demarcation between the small median telocoele and the diocoele, both are included in the cavity of the adult brain known as the third ventricle (Fig 213).

The lateral telencephalic vesicles eventually extend much farther rostrally than the primitive median portion of the telencephalon. The rostral wall of the median part of the telencephalon is known as the *lamina terminalis* (Fig 205, B). This thin portion of the brain wall forms the most rostral part of the brain in the mid-line, and because of the constancy of its relations during development constitutes a valuable landmark (Fig 207). Through its dorsal portion conspicuous fiber bundles cross from one side of the brain to the other, interrelating the olfactory centers. These fibers form the *anterior commissure* which is the earliest of the commissural bundles in the hemispheres to differentiate (Figs 207, G, 210, C).

Once established, the lateral lobes of the telencephalon undergo exceed-

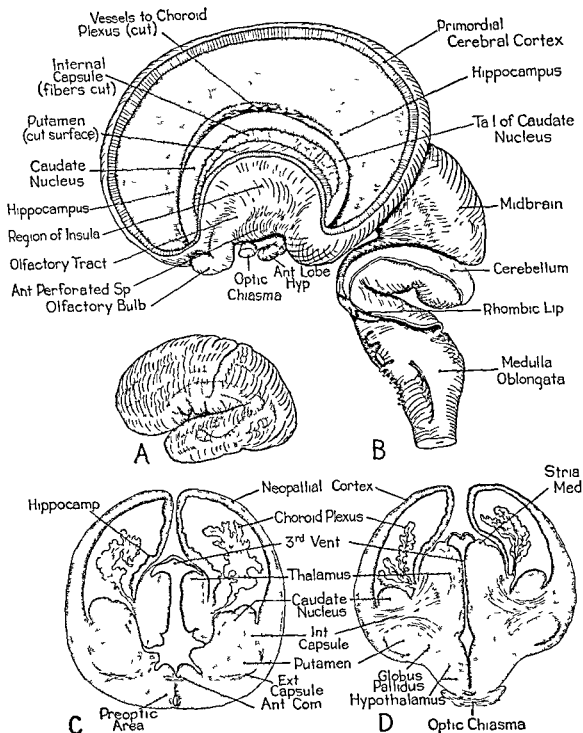


FIG 210 Diagrams showing some of the steps in the development of the corpus striatum A, Schematic transparency showing position of corpus striatum in adult brain (Redrawn after Kreig) B, Lateral view of three-month brain (Modified from a His model) C, D, Sections of the brain of an embryo of approximately same stage of development as model shown in B (Modified from Kodama's illustrations of the brain of a 43 mm embryo) Section diagrammed in C was taken just rostral to optic chiasma, that in D was taken through caudal margin of chiasma

ingly rapid growth, forming the cerebral hemispheres. Their extension rostrally conceals the median portion of the telencephalon, and their even greater expansion dorsally and caudally eventually covers the entire diencephalon and mesencephalon (Fig. 207). The superficial, richly cellular gray layer of the telencephalon is known as the *cerebral cortex*. The immediately underlying regions consist largely of commissural fibers, of fiber paths interrelating one part of the cortex with another (association fibers), and fiber bundles (projection fibers) interconnecting the cortex with other parts of the nervous system. Because these systems of fibers appear whitish in the adult, after they have become medullated, they are said to constitute the *white matter of the hemispheres*. Buried in the white matter, and in part bordering the lateral ventricles, are deep-lying nuclear masses known as the *basal ganglia*. The major⁴ basal ganglia of either hemisphere collectively constitute its corpus striatum.

For purposes of discussion, then, it is convenient to divide the telencephalon into the corpus striatum and the cortical areas. The cortical areas may be subdivided further into olfactory and nonolfactory portions. Since the nonolfactory portions reach their major development late in phylogenetic history, they are appropriately called the neopallial cortex or simply neopallium (= new covering). The olfactory cortex, together with the olfactory bulb and stalk, constitute the *rhinencephalon* (Literally translated, this term means nose-brain). The rhinencephalon reaches its maximum development in lower forms. In primates it is overshadowed by the tremendous growth of the neopallial cortex.

The Corpus Striatum The corpus striatum is developed in the mantle⁵ layer of the ventrolateral walls of the telencephalon. Eventually, it becomes one of the conspicuous internal landmarks in the telencephalic region (Fig. 210, A). It derives its name from the fact that, in certain lower forms, when it is sectioned, its gray matter appears striped by bands of fibers. Its connections are exceedingly complex and many of them are not as yet entirely worked out. Whatever its other activities may be, it is clearly involved in the co-ordination of certain complex muscular activities (Fig. 194, Arc. 6). It also appears to exert a steadying influence on voluntary muscular actions generally, because interference with it is followed by the appearance of muscular tremors during movement.

The corpus striatum, using the term in its inclusive sense, may be subdivided into the *caudate nucleus* and the *lentiform nucleus*. When the caudate nucleus first becomes recognizable, early in the second month, it lies in the floor of the foramen of Monro and tends to bulge in toward the lumen of the ventricles. Later in development it is drawn out in the growing cerebral

⁴ The other structures which are sometimes included as basal ganglia are the claustrum and the amygdala. The *claustrum* is a narrow strip of gray matter between the corpus striatum and the cortex of the insula. The *amygdala* is a mass of gray matter lying deep to the uncus (Fig. 208, E). It is connected with the epithalamus and the hypothalamus and is an olfactory, and probably an olfacto-somatic, correlation center.

hemisphere By the third month it projects conspicuously from the telencephalic floor into the lateral ventricle Rostrally it is partially divided into two ridges by a sulcus, but caudally these ridges tend to merge (Fig 205, B) The expanding caudate nucleus arches rostrocaudally from near the olfactory centers to the caudoventral portion of the hemisphere (Fig 210, B) With further growth all but its rostral part becomes attenuated as its caudal portion is drawn out to an increasing extent into the temporal lobe This long slender part is appropriately known as the tail (cauda) It is, of course, its suggestive configuration that has given the name caudate nucleus to this part of the corpus striatum

Lateral to the caudate nucleus lies the part of the lentiform nucleus known as the *putamen* The putamen is not at first sharply separated from other parts of the hemispheres Later in development fiber tracts appear which almost completely delimit it, although it always retains its connection with the caudate nucleus The putamen (root meaning = husk) constitutes the outer portion of the lentiform (lens-shaped) nucleus (Fig 210) The inner part of the lentiform nucleus is formed by an area which, in the adult, contains many medullated fibers From the whiteness due to its composition this part of the lentiform nucleus is known as the *globus pallidus* (Figs 210, D, 211, D)

The corpus striatum as a whole lies in the part of the telencephalic wall which, in its growth caudad, has come to overlies the diencephalon Where the ventromedial wall of the telencephalon makes contact with the lateral walls of the diencephalon, a secondary fusion occurs (Fig 211, D) Through this region of fusion, fiber tracts develop which interconnect the cerebral cortex and lower centers These fibers constitute the so-called *internal capsule* (Fig 211, D)

Cortical Areas of the Telencephalon Having considered the main steps in the development of the corpus striatum, attention may now be turned to the cortical areas of the telencephalon It will be recalled that the telencephalic cortex can be divided into olfactory and nonolfactory portions At first the cerebral hemispheres are smooth in contour and without striking local differentiations (Fig 206, A) As their development progresses they become much convoluted and certain regional divisions become clearly marked (Fig 206, B-E) A conspicuous fissure in the temporal region, called the rhinal fissure (Fig 208, E), separates the olfactory cortex, medially from the more laterally located nonolfactory portions of the cerebral cortex

OLFACTORY CORTEX This is composed of the rolled-in hippocampus and the adjoining cortical gray Other important parts of the olfactory complex are the olfactory bulb with its stalk, the olfactory tracts, and the anterior perforated space (Fig 210, B) The part of the olfactory complex which first becomes recognizable in the embryo is the *olfactory bulb* This appears in embryos of the sixth week in the form of an enlargement on the ventral surface of each telencephalic vesicle (It is this part of the rhinencephalon on which the leader ends in Fig 205, A) The developing olfactory bulb is at first hollow, containing a cavity which communicates dorsally with the lateral

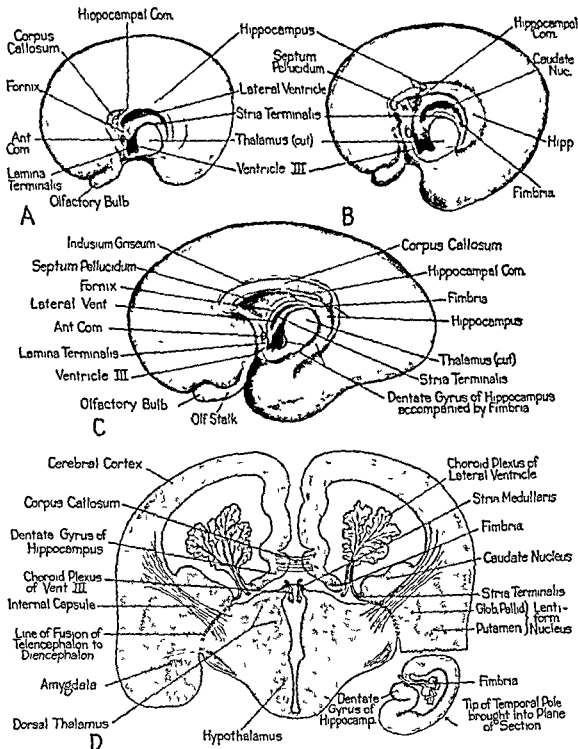


FIG 211 Later development of cerebral hemispheres and their commissures A-C, Medial aspect of right hemisphere at three different ages (Redrawn with some modifications after Streeter in Keibel and Mall) Initial cut separating the two hemispheres from each other was made in the sagittal plane Where cut was extended across thalamus to separate hemisphere from brain-stem, it slanted laterad A, At 80 mm (about three months) B, At 95 mm (early in fourth month) C, At 150 mm (early in fifth month) D, Schematized cross-section of the hemispheres showing corpus callosum and secondary fusion of telencephalon and diencephalon (Based in part on Broman)

ventricle. The outgrowth thus established tends to extend distally, forming a lengthening olfactory stalk carrying the olfactory bulb at its end (Fig 211, A-C). As the stalk becomes more elongated and attenuated, it loses its lumen. At the same time the lumen of the bulb becomes almost completely obliterated.

Immediately caudal to the olfactory bulb a primordial elevation thickens to form olfactory centers in the basal and medial portions of the walls of the hemisphere. Conspicuous among these centers is the *anterior perforated substance (space)* (Fig 210, B) which gets its name from the presence of many small holes caused by the penetration of blood vessels. The "perforations" remaining when these vessels are pulled out in the removal of the meninges are conspicuous superficial markings in front of the optic chiasma on either side (They are shown but not labeled in Fig 208, D, E).

The hippocampus early takes on an arched configuration following the expansion of the telencephalic lobes. The rostral limb of the hippocampus rests on the medial part of the anterior perforated substance. Seen in the brain of a three-months embryo with the hemisphere opened from the lateral side the hippocampus arches rostrally and then dorsally around the interventricular foramen. It then curves back, forming the ventromedial portion of the pallium (Fig 240, B). Along its ventral border is the developing choroid fissure through which vessels push to form the choroid plexus of the lateral ventricle. Caudally the hippocampus follows the curve of the caudate nucleus into the temporal pole of the growing hemisphere. As the temporal lobe recurves below the parietal lobe and grows forward (Fig 206, L), the original caudoventral portion of the hippocampus is carried forward with it. As we shall see shortly, when the development of the corpus callosum is discussed, the rostradorsal portions of the hippocampus are rolled back during the development of this *neopallial commissure*. The fiber tract, however, which connects the hippocampal cortex with the diencephalon, follows the original line of hippocampal curvature along the choroid fissure and above and rostral to the interventricular foramen. This tract is the so-called *forinx* (Fig 211, C) which passes ventrocaudally from the region of the interventricular foramen to the mammillary body in the hypothalamus.

NONOLFACTORY (NEOPALLIAL) CORTEX. In primates the nonolfactory (neopallial) cortex completely overshadows the rhinencephalon which constitutes such a conspicuous portion of each hemisphere in lower mammals. This change in proportion is due in part to a reduced importance of the olfactory sense, but more especially to the tremendous growth of the nonolfactory (neopallial) cortex in primates, especially in man. In the neopallial cortex are located suprasegmental centers concerned with memory, voluntary action, and inhibitory control (Fig 194, Arc 7).

As the cortex develops, its area is so greatly expanded that it is thrown into folds (convolutions, gyri) with grooves (fissures, sulci) between them. All the principal convolutions and fissures are named and the centers for various special functions have been located with considerable accuracy in specific areas. It would carry us beyond the scope of this book, however, were we to

attempt to do more than become familiar with a few of the more important regions of the cerebral hemispheres

The first conspicuous marking to appear on the lateral aspect of the hemisphere is the *Sylvian fossa* (Fig 206, D) This depression is recognizable as early as the third month and is progressively more sharply circumscribed as the surrounding areas become elevated The slowly growing cortex forming the floor of the Sylvian fossa, lateral to the corpus striatum (Fig 210, B) is known as the *insula* (*island of Reil*) The more rapidly growing surrounding areas extend over it constituting covering folds known as opercula There are three opercula—frontal, parietal, and temporal—each a part of the lobe designated by its name The approximation of the opercula with each other gradually conceals the insula The lateral (Sylvian) fissure marks the line of their contact (Fig 206, E) An “open” insula in an adult is, therefore, indicative of a failure of normal development in the parts of the cortex constituting the opercula In the ordinary course of events the frontal operculum is the last to acquire its full development Defective development of this opercular region is clinically of considerable interest because certain association areas in the frontal operculum are concerned with speech It is believed by many workers that the dominant center for articulate speech in a right-handed person is on the left, and in a left-handed person presumably on the right

On the upper margin of the temporal operculum, in a region just failing to show in a lateral view, is the auditory projection area To this region are brought impulses from the receptive mechanism for sound in the internal ear (cochlea) There is good evidence that this auditory projection area has a functional pattern corresponding to the cochlear pattern concerned with discrimination of pitch

During the fifth and sixth months of development the central, parieto-occipital, and calcarine fissures become recognizable The *central fissure* indicates the boundary between frontal and parietal lobes (Fig 206) This fissure is an even more important landmark from the functional than from the descriptive standpoint The gyrus immediately rostral to the central fissure (*precentral gyrus*) contains localized centers for the voluntary control of motor responses for much of the head, the neck, and the body The gyrus immediately caudal to the central fissure (*postcentral gyrus*) contains the corresponding localized sensory centers of pain, temperature, touch, and *proprioception* Impulses of these types collectively constitute what is frequently designated as somesthetic sensibility

The lateral part of the *parieto-occipital fissure* lacks the striking functional significance of the central fissure, and is chiefly of importance, as its name implies, in helping to establish the boundary between the parietal and the occipital lobes (Fig 206, E) On the medial aspect of the hemisphere, in conjunction with the calcarine fissure, it delimits a wedge-shaped cortical area known as the *cuneus* (Fig 207, G) The cuneus is one of the important regions concerned with visual association

Like the central fissure, the *calcarine fissure* is an important landmark from

the functional standpoint. Along the two lips of the calcarine fissure lie the *visual receptive (projection) areas of the cortex*. It is in this region that the images thrown on the retina are brought into consciousness (Fig. 236). The inferior visual fields are projected on the superior lips of the calcarine fissures and the superior visual fields on the inferior lips. The region of the retina responsible for the sharpest visual discrimination (the macular area of the retina) has its projection area located at the most caudal extremity of the calcarine fissure. It is for this reason that blows on the back of the head may, if severe enough to produce local hemorrhage in the underlying cortex, cause varying degrees of visual impairment.

In the foregoing paragraph some of the more important cortical centers have been located. The motor and sensory somesthetic areas, together with the visual, olfactory, and auditory centers, are spoken of as "*projection areas*." The term projection in this connection has come to imply the transmission of impulses in either direction between a cortical and a noncortical area with the retention of a specific pattern. Thus visual impulses may be "projected" from the retina to form a corresponding pattern in the visual cortical centers along the calcarine fissure. Likewise from localized centers in the cortex, motor impulses may be projected to lower centers in accordance with a specific pattern.

Bordering the projection areas are primary *association areas* dominated by the impulses traversing the projection pathways. Such areas also intercommunicate with other cortical areas by association paths, and with lower centers by way of projection paths. In addition, in primates and particularly in man, secondary association areas are developed in the temporal, parietal, and especially in the frontal cortex. The high development of the frontal association areas in man is one of the most striking differences between the human brain and that of higher apes. It is the interconnection of such association areas in the cortex that provides the physical basis for memory, for intelligent response to past experience, and for constructive social responsibility.

Histogenesis of Cortex In the cerebral hemispheres, as in other parts of the developing central nervous system, the walls of the young brain show the characteristic ependymal, mantle, and marginal zones (Fig. 212, A). The first place that neopallial cortical differentiation becomes recognizable is in the region of the insula. Differentiation extends thence to other cortical areas. Beginning in the third month large numbers of neuroblasts migrate peripherally to form a layer of young nerve cells (predominantly young pyramidal cells) beneath the primitive marginal zone. This layer of neuroblasts close to the surface of the brain constitutes the primordial cortical gray (Fig. 212, B). As development progresses there is a marked increase in the number of fibers in the layer intermediate between the primordial cortex and the neuroblasts (inner nuclear layer, Fig. 212, C) that have remained adjacent to the ependymal zone. During this process most of the neuroblasts have moved out of the fibrous layer, although occasional strands of cells or scat-

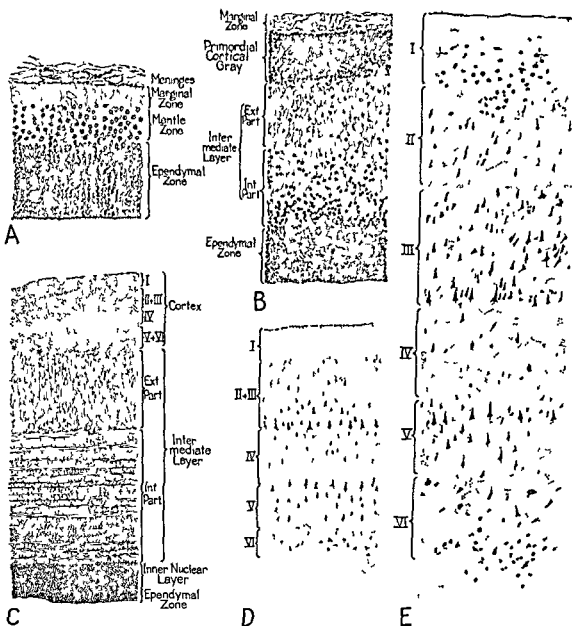


FIG 122 Histogenesis of cerebral cortex A, Entire thickness of telencephalic wall from a human embryo at beginning of the eighth week ($\times 200$) B, Entire thickness of telencephalic wall in an embryo of the tenth week ($\times 125$) C, Entire thickness of telencephalic wall in an embryo of the fourteenth week ($\times 225$) D, Cortex only, from fetus of about six months (Redrawn, $\times 33$, from Brodmann) E, Adult parietal cortex (Redrawn, $\times 40$, from Huber, Kappers, and Crosby) Roman numerals used in labeling of C-E stand for the cortical layers (I) Molecular layer (lamina zonalis of Brodmann), (II) outer granular layer, (III) pyramidal cell layer (lamina pyramidalis), (IV) inner granular layer, (V) ganglion cell layer (lamina ganglionaris), and (VI) multi-form cell layer (lamina multiformis)

tered neuroblasts remain until after birth. With its myelination this fibrous layer becomes the massive white layer of the hemisphere.

During the fourth and fifth months the peripheral zone of neuroblasts constituting the primordial cortical gray gradually subdivides into an outer and an inner band separated from each other by a layer containing only scattered small neuroblasts (Fig. 212, C). This less cellular zone constitutes the primordial internal granular layer (Fig. 212, C, IV) of the cortex. The cellular band superficial to the internal granular layer (Fig. 212, C, II and III) and the cellular band deep to this layer (V and VI) each differentiates secondarily into two layers. As shown in Fig. 212, D, this separation occurs somewhat earlier in the band deep to the granular layer (infragranular gray). When, by the seventh month, the supragranular gray has also divided and become differentiated into the external granular (II) and the pyramidal layer (III), a six-layered cortex is formed with its outermost layer (I) constituted by the original marginal zone. By modifications of these six basic layers the characteristic patterns of the various specialized regions of the neopallial cortex are established. (See, for example, the sensory cortex from the human postcentral gyrus diagrammed in Fig. 212, E.) Neuroanatomists now recognize some 80 to 90, or more, characteristic local variants of the underlying basic pattern.

Commissures of the Telencephalon In connection with the lamina terminalis, mention was made of the *anterior commissure*. It will be recalled that this group of decussating fibers is primarily concerned with the interrelation of olfactory centers in the hemispheres. It is one of the earliest of the commissures to appear and constitutes a valuable landmark in dealing with the developing brain (Figs. 207, G, 210, C, 211, A-C).

Another group of crossing fibers in the hemispheres which is also concerned with the olfactory sense is the *hippocampal commissure*. As its name implies, its fibers interconnect the hippocampi of the two sides. It first makes its appearance in the third month in the thin rostral wall of the third ventricle, dorsal to the anterior commissure (Fig. 211, A). Its fibers are accompanied by projection fibers from the hippocampus which pass partly to the epithalamus (by way of the stria medullaris, Fig. 211, D) but more conspicuously to the hypothalamus as the so-called fornix (Fig. 211, A-C). With the growth of the corpus callosum, which will be discussed directly, the hippocampus is gradually carried backward and downward into the temporal pole of the growing cerebral hemisphere. In this process the hippocampal commissure is shifted caudad until it ultimately comes to lie beneath the caudal end of the corpus callosum (Fig. 211, A-C).

The third commissural system of the telencephalon is the so-called *corpus callosum* which is a massive system of fibers interconnecting the nonolfactory areas of the cortex. It is formed in an area of secondary fusion between the two hemispheres and is best developed in the human brain in which the neopallial cortex reaches its maximum. The corpus callosum is first recognizable during the third month in the area rostral and dorsal to the hippocampal commissure.

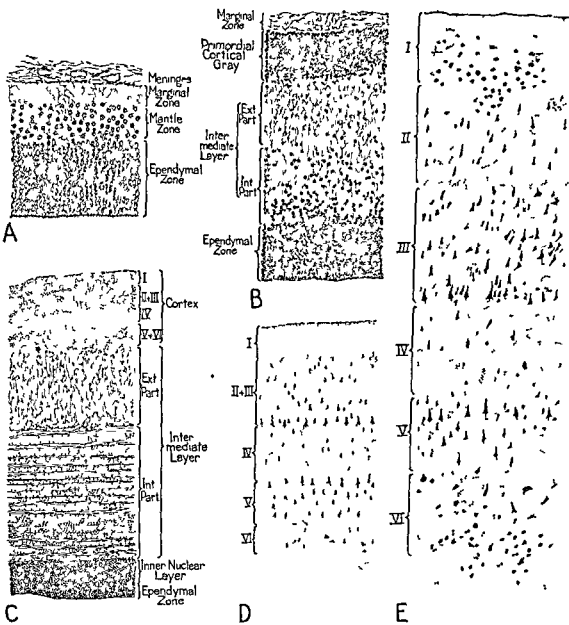


FIG 212 Histogenesis of cerebral cortex A, Entire thickness of telencephalic wall from a human embryo at beginning of the eighth week ($\times 200$) B, Entire thickness of telencephalic wall in an embryo of the tenth week ($\times 125$) C, Entire thickness of telencephalic wall in an embryo of the fourteenth week ($\times 225$) D, Cortex only, from fetus of about six months (Redrawn, $\times 33$, from Brodmann) E, Adult parietal cortex (Redrawn, $\times 40$, from Huber, Kappers, and Crosby) Roman numerals used in labeling of C-E stand for the cortical layers (I) Molecular layer (lamina zonalis of Brodmann), (II) outer granular layer, (III) pyramidal cell layer (lamina pyramidalis), (IV) inner granular layer, (V) ganglion cell layer (lamina ganglionaris), and (VI) multi-form cell layer (lamina multiformis)

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The third commissural system of the telencephalon is the so-called *corpus callosum* which is a massive system of fibers interconnecting the nonolfactory areas of the cortex. It is formed in an area of secondary fusion between the two hemispheres and is best developed in the human brain in which the neopallial cortex reaches its maximum. The corpus callosum is first recognizable during the third month in the area rostral and dorsal to the hippocampal commissure.

(Fig 211, A) It is bordered in part by hippocampal gray. In its growth the corpus callosum extends both rostrally and caudally (Fig 211, A-C) until it assumes its characteristic definitive configuration. This growth of the corpus callosum entails changes in the position and the molding of certain associated structures. Conspicuous among these changes is the previously mentioned backward and downward shifting of the main mass of the hippocampus on either side. In this shift of the hippocampal gray matter, the associated projection tract (fornix) is pulled out along the course of the migration (cf the length and relations of the fimbria and fornix in Figs 211, A-C). A record of this process is left in the form of a thin film of hippocampal gray (gray stripe of Lancisi or indusium griseum, Fig 211, C), together with its associated fibers (white stripe of Lancisi) recognizable in the adult along either side of the dorsal surface of the corpus callosum.

Rostral to the hippocampal commissure in the angle between it and the forward-growing part of the corpus callosum is a small area of the hemisphere wall. With the continued growth of the corpus callosum and the backward shift of the hippocampal commissure this area becomes greatly thinned to form the so-called *septum pellucidum* (Fig 211, B). The thin septa pellucida of the two hemispheres, situated between the corpus callosum and the fornix, may fuse partly or completely with each other. If the fusion is not complete a slitlike space of variable extent remains as the so-called *cavum septi pellucidi*.

VENTRICULAR SYSTEM OF THE BRAIN, CHOROID PLEXUSES, AND CEREBROSPINAL FLUID

Brain Ventricles As has been indicated already in discussing the various parts of the nervous system, the ventricles of the adult brain are derived by local modifications of the primary lumen of the neural tube. In the spinal cord the lumen gradually becomes reduced to form the central canal (Fig 201). The original rhombocoel remains as a continuous cavity in spite of the specialization of its walls to form separately differentiated met- and myelencephalic structures. Caudally the rhombocoel is narrow, and directly continuous with the central canal of the spinal cord. Its rostral three-fourths widens out to constitute the *fourth ventricle* (rhomboid fossa) with its striking lateral recesses (Fig 213, A-D). Following the system of brain cavities rostrad, one finds the original mesocoel greatly narrowed by the growth of the surrounding walls to form the *cerebral aqueduct* (of Sylvius). This slender passage connects the fourth ventricle with the slitlike *third ventricle* formed by the narrowing of the original diocoel and the small median portion of the telocoel with which it is continuous. It will be recalled that the great bulk of the telencephalon early comes to be made up of its lateral vesicles. The lumen in each lateral vesicle constitutes the primordium of a lateral ventricle. These two lateral cavities are spoken of as the *first and second ventricles* of the brain. There is no established convention as to whether the first ventricle is that on the right or the left.

With the growth of the cerebral hemispheres the lateral ventricles take

on a highly characteristic configuration. They at first balloon out laterad and rostrad (Fig 213, B). The rostral extension on either side increases and becomes modified in shape to form the anterior horn of the adult ventricle (Fig 213, B-E). Coincidentally, there is an even more marked backward growth of ventricles forming the body and the beginning of the posterior and

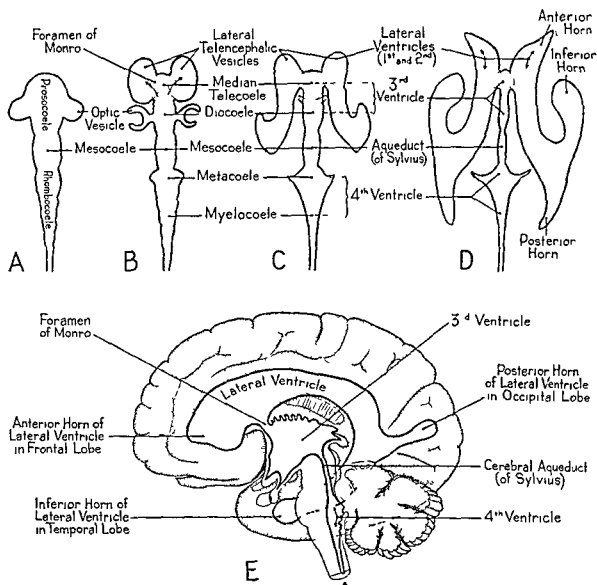


FIG 213 Schematic diagrams showing development of cerebral ventricles from cavities of embryonic brain A, Primitive three-vesicle stage B, Early five-vesicle stage C, Expansion of lateral telencephalic vesicles (Modified from Broman) D, Final arrangement—schematic—viewed from above (Modified from Broman) E, Final arrangement as viewed from the side. Contours of the brain are indicated for orientation (Modified from Fischel)

the inferior horns. The posterior horn is extended with the growth of the occipital pole of the hemisphere. With the growth of the temporal pole, the inferior horn is carried lateralward, downward, and forward with finally a tendency to recurve mesially (Fig 213). It will be recalled that the openings from the median portion of the telocoel which connect with each of the lateral ventricles are called the *foramina of Monro*. As the brain takes on its definitive configuration, these openings connecting the third ventricle with the two

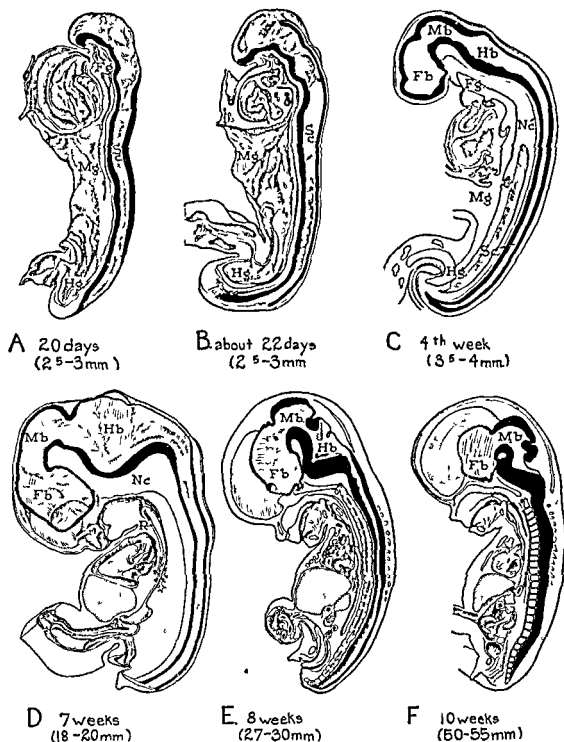
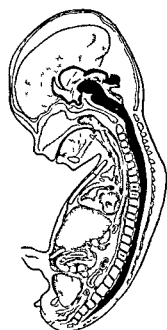
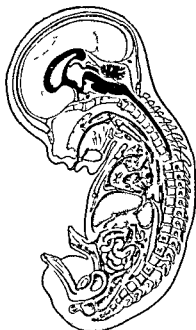


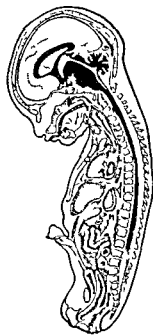
FIG. 214 Semichematic diagrams graphically summarizing some of the main steps in the development of the nervous system. To facilitate comparisons body length has been held constant and the nervous system drawn to proper



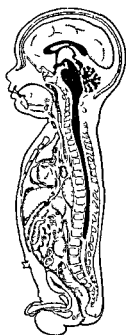
G 12 weeks
(75-80mm)



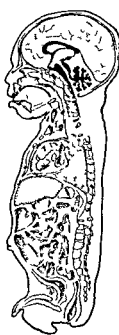
H 20 weeks
(180-185mm)



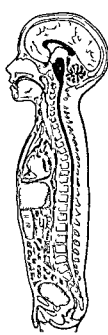
I 24 weeks
(225-235mm)



J 34 weeks



K Neonatal



L 6 years



M Adult

proportion in the body outlines (Thirteen stages selected from the Scammon-Lewis series in Morris "Human Anatomy")

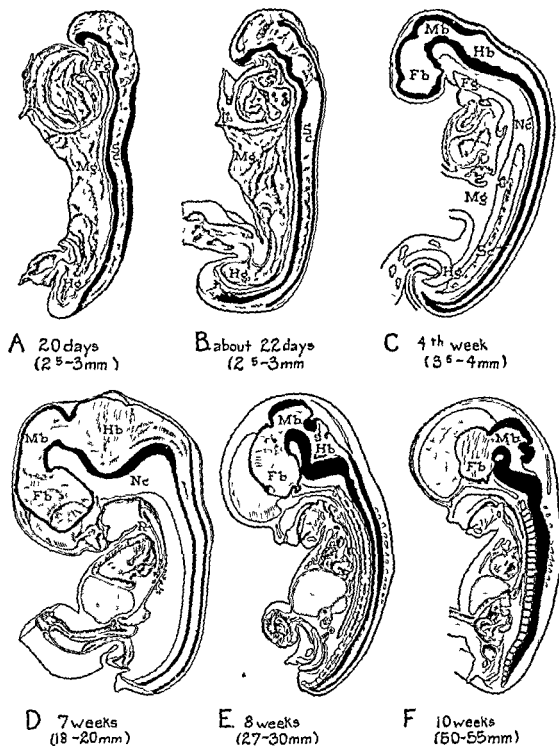


FIG 214 Semichematic diagrams graphically summarizing some of the main steps in the development of the nervous system. To facilitate comparisons body length has been held constant and the nervous system drawn to proper

From the above it is seen that the cranial nerves are built on the same general plan as the spinal nerves. The cranial nerves have lost most of their primitive segmental arrangement and have become very highly specialized. Some of them contain both afferent and efferent fibers, as is the case with the spinal nerves. In such instances they are called mixed nerves. Some contain only afferent fibers and others are made up predominantly of efferent fibers. No single cranial nerve contains all the types of fibers that occur in the cranial nerves as a group (Fig. 215).

CRANIAL NERVES

In dealing with the spinal nerves we saw that they have types of fibers, general somatic afferent, general somatic efferent, general visceral afferent, and general visceral efferent (Fig. 210). In the cranial nerves we find these same types of neurons and in addition we have some very specialized distribution and more specialized functions. The eye, for example, is a very highly differentiated and sharply localized sense organ concerned with hearing. The fibers arising at such receptive exclusiveness are set apart from the general somatic afferent category by designating them as *special somatic afferent fibers*. In the taste buds set on a tongue which are concerned with carrying gustatory impulses to the brain. These are called *special visceral afferent fibers*. As was pointed out in the preceding chapter, the musculature in the facial, pharyngeal, and laryngeal regions differs from other visceral musculature in that it is striated muscle of brachiomeric origin. Therefore, the motor fibers to it are distinguished from other visceral motor fibers by calling them *special visceral efferent nerves*. In this account the nerves to the muscles of the eye and the tongue are regarded as *general somatic efferent fibers*, although certain writers prefer to call them special somatic efferent fibers because they are components of cranial rather than of spinal nerves.

The spinal nerves are segmentally arranged and all of them are built on the same general plan. The cranial nerves have lost most of their primitive segmental arrangement and have become very highly specialized. Some of them contain both afferent and efferent fibers, as is the case with the spinal nerves. In such instances they are called mixed nerves. Some contain only afferent fibers and others are made up predominantly of efferent fibers. No single cranial nerve contains all the types of fibers that occur in the cranial nerves as a group (Fig. 215).

In both spinal and cranial nerves, afferent fibers arise from cell bodies outside the neural tube (Cf Figs. 200, 215). Thus the cranial nerves that carry afferent fibers have ganglia composed of clusters of their cell bodies.

lateral ventricles become relatively narrower, but they still retain their original name

Choroid Plexuses It should perhaps be emphasized that throughout the local regional differentiation just described, continuity is retained between the cavities within the various parts of the brain and the spinal cord. In these cavities there is a fluid which differs in cell content and in chemistry from either blood or lymph. This is the so-called *cerebrospinal fluid*. Although this fluid may be supplemented by direct seepage from the vascular system, it is believed to be formed chiefly in special areas known as the *choroid plexuses*. There are certain regions along the roof of the fourth, third, and lateral ventricles in which neither fiber tracts nor nuclear masses develop. Consequently the walls here remain thin, consisting merely of a layer of ependymal cells backed by a delicate basement membrane. In each of these three regions local blood vessels form a rich capillary plexus (choroid plexus) which lies close against the thin ependymal roof. These capillaries push the ependymal membrane ahead of them into tufts and folds which bulge into the ventricular lumen. Thus is formed a highly specialized secretory mechanism in which modified ependymal cells extract fluids from a vascular plexus and pass their secretory products into the ventricular lumen. The fact that this is a true secretory process rather than a mere filtration is suggested by the granules which develop in the ependymal cells, and confirmed by the fact that the cerebrospinal fluid has its own characteristic chemical composition which is different from that of either blood or lymph.

Circulation of the Cerebrospinal Fluid Disregarding minor local resorption, it is clear that in man the major part of the cerebrospinal fluid follows a characteristic and definite course. The fluid contributed by the choroid plexuses of the lateral ventricles passes through the foramina of Monro into the third ventricle. Here its volume is increased by fluid secreted in the choroid plexus of the third ventricle. From the third ventricle the cerebrospinal fluid passes by way of the narrow aqueduct of Sylvius into the fourth ventricle. Here it is further augmented by the activity of the choroid plexus of this ventricle. In the roof of the lateral recesses are openings from the fourth ventricle into spaces in the meningeal layers investing the central nervous system. Through these openings, the *foramina of Luschka*,⁵ the cerebrospinal fluid leaves the brain cavities and enters the so-called *subarachnoid space(s)*. This space in reality consists of a meshwork of irregular channels by way of which fluid may pass either backward into the meninges about the spinal cord, or into the cerebral meninges. In the cerebral region there are certain areas (e.g., above and below the cerebellum and below the midbrain) where the natural configuration of the brain and cranium favors larger intrameningeal spaces. In such regions, called cisterns, the cerebrospinal fluid collects in relatively larger

⁵ Some observers believe there is in addition to the foramina of Luschka a median opening in the roof of the fourth ventricle, the foramen of Magendie. There is, however, considerable evidence that this median foramen may be an artefact due to tearing of the roof in the preparation of the material.

situated just outside the brain wall (Fig 199) Likewise the efferent fibers in the spinal and the cranial nerves are similar in that they arise from cell bodies inside the wall of the neural tube In the spinal nerves these cell bodies lie in the ventral and lateral horns of the gray matter of the cord In the cranial nerves their position is homologous for they lie in clusters (nuclei) in the basal plate of the brain wall (Cf Figs 200, 215)

If one considers these general facts it becomes apparent that, although the cranial nerves differ from the spinal nerves in certain respects, both contain afferent and efferent neurons and both show the same characteristic differences in the positions of the cell bodies associated with these two components Put in another way, the cranial and spinal nerves contain essentially the same kinds of components although they are divergently specialized and differently grouped It will be helpful to keep this in mind in considering the various cranial nerves

Olfactory Nerve (I)⁶ Unlike other sensory nerves, the olfactory nerve lacks a ganglion It is peculiar, also, in that all its fibers are nonmedullated These fibers are the axonic processes of neurons, the cell bodies of which are situated within the epithelial layer lining the olfactory pits Thence the axons grow centripetally into the olfactory bulbs In so doing they pass through multiple small foramina in the developing cribriform plate of the ethmoid (Fig 168, D, 227, E, 229, D) In the olfactory bulbs the fibers of the nerve terminate in synapse with other neurons (mitral cells) which relay the impulses along the olfactory tracts to centers in the rhinencephalon On a functional basis the neurons composing the olfactory nerve are usually classified as special visceral afferent Regarding them as visceral rather than somatic stresses the importance of the olfactory sense in connection with eating

Optic Nerve (II) Although customarily designated as the second cranial nerve, the optic nerve is really not a nerve in the strict sense It will be recalled that the optic cup arises as an outgrowth of the lateral wall of the prosencephalon The sensory layer of the retina is, therefore, a specialized portion of the brain wall and the nerve fibers arising from its ganglion cells really form a fiber tract within the central nervous system, rather than a true nerve This situation is emphasized by the fact that the human optic nerve, like other parts of the brain, does not effectively regenerate following injury The optic nerve fibers, then, develop as processes of neuroblasts situated in the sensory layer of the retina, in close association with its *photosensitive cells* These fibers leave the optic cup by way of the choroid fissure, then traverse

⁶ There are two small nerves closely associated peripherally with the olfactory nerve One of these (nervus terminalis) can be traced to the rostral part of the septal wall of either nasal chamber, and followed back through the cribriform plate to the median telencephalon near the anterior commissure Its central relations have not been ascertained and its function is not clearly understood In adult primates it is almost vestigial, but in human embryos it is relatively more easily traced (McCotter 1915)

The other nerve (vomeronasal) has been demonstrated in man only in the embryo As its name implies, it is associated peripherally with the vomeronasal organ (of Jacobson) It can be traced through the cribriform plate along with the nervus terminalis, and terminates in the accessory olfactory bulb

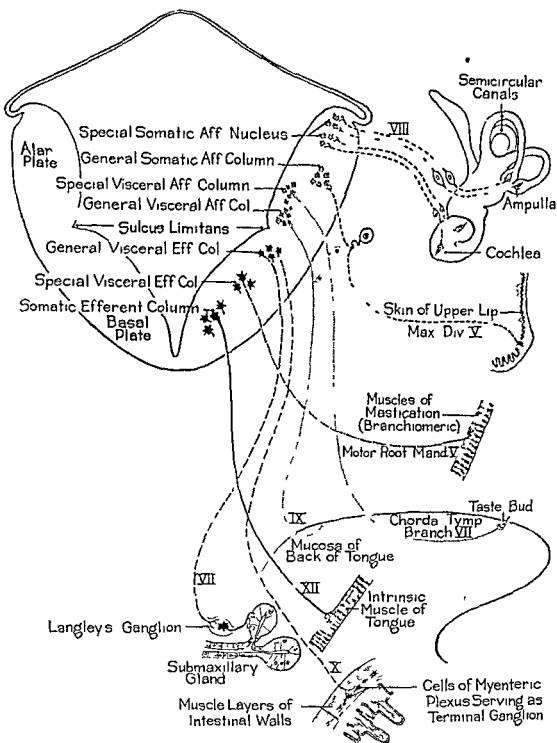


FIG 215 Diagram showing examples of various types of components found in cranial nerves. It should be emphasized that this is a composite, schematic figure. No one cranial nerve has all the components here shown.

cell bodies in the ganglion, and their termination in the nucleus of the descending root of the fifth nerve and its chief sensory nucleus (Fig 219, B, 220, B-D) Being of cutaneous origin, they are exteroceptive. There are also motor fibers in the mandibular division supplying the muscles of mastication. Because these muscles are of branchiomeric origin, the fibers supplying them are classified as special visceral efferent. These motor fibers arise from a nucleus in the basal plate of the pons (Fig 219, A). The motor fibers are accompanied by a relatively large proprioceptive component. These proprioceptive somatic afferent neurons are peculiar in that their cells of origin are located within the central nervous system instead of lying in an external sensory ganglion as is usual with neurons of this category. Their cell bodies constitute a nuclear mass (nucleus of the mesencephalic root of the fifth nerve) which extends rostrad, into the mesencephalon, from the level of entrance of the trigeminal nerve into the pons.

Abducens Nerve (VI) The abducens nerve takes its name from the fact that it controls the external rectus muscle, contraction of which makes the eyeball rotate outward. The abducens nucleus lies in the basal plate of the myelencephalon (Fig 220, E, F). From its cells, fibers arise and course ventrally to emerge just caudal to the pons. These neurons are somatic efferent in type. As was the case with the third nerve, there are believed to be proprioceptive fibers in the sixth present along with these motor fibers.

Facial Nerve (VII) The facial nerve is primarily efferent but the presence of the geniculate ganglion on its root shows that it carries also some afferent fibers. A large part of its sensory fibers pass by way of the chorda tympani branch to join the lingual branch of the mandibular division of the fifth nerve (Figs 216-218). These fibers are concerned with the sense of taste and are classified as special visceral afferent. In addition to these fibers there are a few general somatic afferent fibers supplying a small cutaneous area on the inner aspect of the external ear.

The motor fibers of the seventh nerve arise from the facial nucleus situated in the basal plate of the myelencephalon. This nucleus is first differentiated near the floor of the fourth ventricle in relation with the general visceral efferent column (Fig 220, E). Its fibers grow outward while it lies in this primitive position which is an indication of its primary phylogenetic relations. Later in development the facial nucleus migrates ventrolaterad causing its nerve fibers to follow a strikingly bent course. This bend in the facial nerve is known as its genu (knee) (Fig 220, F). In this migration the cell bodies have come into closer positional relations with the source from which they pick up their impulses. This migration in effect shortens the dendrites, which are less efficient conductors, and lengthens the axons, which are better conductors. This migration of nerve cell bodies toward the centers from which their dominant impulses are initiated is known as *neurobiotaxis*. The nerve fibers arising thus in the facial nucleus supply primarily the muscles of facial expression. It will be recalled that this group of muscles arises in connection with the hyoid arch (Figs 189-193). They belong, therefore, in the group of

the grooved ventral aspect of the optic stalk and enter the brain in the diencephalic floor. At their point of entrance some of the fibers in each optic nerve cross to the other side so that some fibers from each eye go to each side of the brain. The region of this crossing is known as the optic chiasma (Fig. 236). From the chiasma the fibers pass along the lateral walls of the diencephalon to the visual centers of the thalamus and midbrain. (See the section on the eye in the following chapter.) It is customary to classify the optic nerve fibers as special somatic afferent.

Oculomotor Nerve (III) As its name implies, the oculomotor nerve contains motor fibers to muscles moving the eye. The cluster of neuroblasts from which it arises is located in the basal plate of the mesencephalon. Its fibers have relations comparable to those indicated in Fig. 215 for the hypoglossal fibers leading away from the somatic efferent nucleus to the intrinsic muscles of the tongue. Emerging from the floor of the mesencephalon (Fig. 199), they pass directly to the orbital region. They innervate (1) the inferior oblique, (2) the superior, inferior, and medial rectus muscles of the eyeball, and (3) the levator muscle of the upper lid. These motor fibers are classified as general somatic efferent. There are proprioceptive endings in the eye muscles giving one a sense of the position of the eyeballs. It seems probable that the afferent fibers from these endings accompany the fibers of the motor nerve supplying the muscle in question. Such fibers would be classified as general somatic afferent—proprioceptive. There are also preganglionic fibers en route to the ciliary ganglion where they synapse with postganglionic fibers to the circular muscle of the iris and to the ciliary muscle. These are classified as general visceral efferent—"visceral" because the muscle supplied is smooth, and because the fibers in question are part of the autonomic nervous system.

Trochlear⁷ Nerve (IV) The trochlear nerve is primarily a motor nerve to the superior oblique muscle of the eye. Its nucleus of origin, like that of the third nerve, is located in the basal plate of the mesencephalon. It is peculiar in that its fibers do not leave directly from the ventral walls of the brain as usually happens in a somatic motor nerve. Instead they pass to the dorsal wall of the mesencephalon and cross before emerging in the notch between mesencephalon and metencephalon (Fig. 199). These fibers are somatic efferent. Like the third nerve the fourth probably carries some general somatic afferent fibers of proprioceptive type from the superior oblique (trochlear) muscle.

Trigeminal Nerve (V) The trigeminal nerve takes its name from the fact that it has three main divisions: the ophthalmic, the maxillary, and the mandibular (Figs. 216–218). As is indicated by its large semilunar (Gasserian) ganglion, the fifth nerve has great numbers of sensory fibers. These are general somatic afferent fibers of the type shown in Fig. 215 with their

⁷ Not even sufficient knowledge of Greek to recognize in the name trochlear the root meaning 'pulley' is of much help in understanding its significance. One has to find that the nerve takes its name from an old appellation of the superior oblique muscle to which it runs. This muscle was formerly known as the trochlear muscle because its tendon passes through a pulleylike fibrous loop attached to the eye socket.

branchiomeric muscles, and the nerve fibers to them belong in the special visceral efferent category

In addition to the special, there are general visceral efferent components in the seventh nerve. These are preganglionic neurons for the parasympathetic

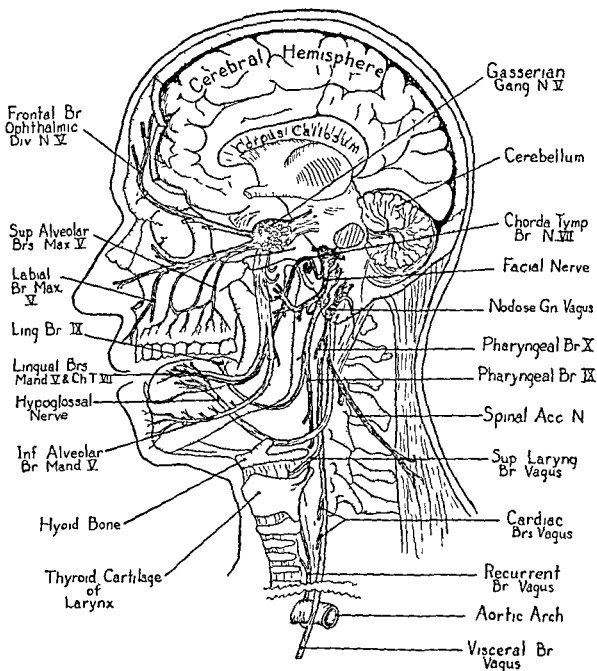


FIG 218 Schematic diagram showing trunks and main branches of the cranial nerves in the adult (Redrawn, with some modification, from Corning) The color scheme corresponds with that of Figs 216 and 217

chains to the lacrimal gland by way of the sphenopalatine ganglion, to the submaxillary gland by way of Langley's ganglion lying in the stroma of the gland near its main duct (Fig 215), and to the sublingual gland by way of the submaxillary ganglion

Auditory Nerve (VIII) At first the ganglionic mass from which the fibers of the eighth nerve arise is closely associated with the geniculate ganglion

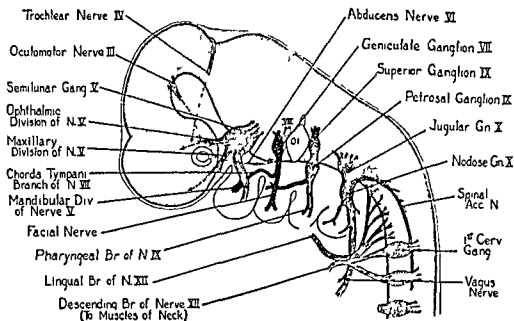


FIG. 216 Semischematic diagram showing arrangement of cranial nerves in embryos of about five weeks (Redrawn with some modification from Corning) The arbitrary color scheme used in this figure is retained in the two following illustrations on the cranial nerves, Figs 217 and 218

In Figs 189, 190, 192, and 193 the developing muscles of this region have been diagrammed using the same series of colors to indicate the nerves supplying the muscles. These two groups of illustrations should be carefully compared

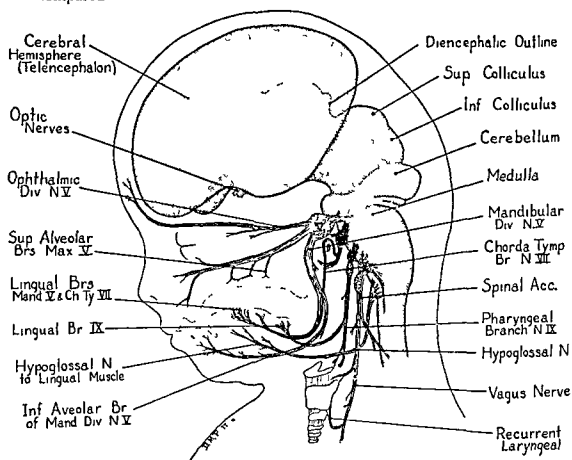


FIG. 217 The arrangement of the cranial nerves in embryos of about 11 weeks' fertilization age (50-60 mm C-R) The color scheme corresponds with that of Fig 216

of the seventh nerve. Gradually these ganglia become entirely distinct. Still later the ganglion of the eighth nerve divides into two parts—a vestibular ganglion and a spiral ganglion (Fig. 240). With the division of the ganglion, the nerve fibers arising from its cells become grouped into two main bundles, one associated with each ganglion. Meanwhile, the otic vesicle has differentiated into two distinct parts—the cochlea, which is the organ of hearing, and the group of semicircular canals which constitute an organ of equilibration. The spiral ganglion and the cochlear branch of the eighth nerve become associated with the auditory part of the mechanism. The vestibular ganglion and its branch of the eighth nerve become associated with the semicircular canals. The auditory and equilibratory fibers have the general relations indicated in Fig. 215. They both belong in the special somatic afferent category. Because the auditory fibers are concerned in transmitting impulses which have been initiated in the surrounding environment, they are subclassified as *exteroceptive*. The vestibular fibers are concerned with impulses originating in the ampullae of the semicircular canals and the maculae of the sacculus and the utricle which are concerned with controlling body position. They are, therefore, classified as special somatic afferent—*proprioceptive*.

Glossopharyngeal Nerve (IX) The glossopharyngeal is a mixed nerve, but by far the greater number of its fibers are sensory. The ganglion cells from which these sensory fibers arise are grouped in two clusters, one near the root of the nerve (superior ganglion), and one farther peripherally on its course (petrosal ganglion) (Figs. 216-218). The cell bodies in the superior ganglion give rise to fibers which innervate a small inconstant cutaneous area of the external ear. These neurons are therefore general somatic afferent—*exteroceptive*. The petrosal ganglion contains cell bodies giving rise to visceral afferent fibers. Some of these, being concerned with general sensibility in the region of the root of the tongue and the oropharynx, are general visceral afferent. Other fibers innervate taste buds in the root of the tongue and are special visceral afferent.

The glossopharyngeal nerve, like the facial, contains both special and general visceral efferent components. The special visceral efferent fibers arise from a nuclear column (nucleus ambiguus) common to this component in the glossopharyngeal, the vagus and the bulbar (brain-stem) portion of the accessory nerve (Fig. 219, A). These fibers in the ninth nerve supply the stylopharyngeus muscle (Figs. 189, 190, 193). The general visceral efferent fibers of the ninth nerve arise from cells in the inferior salivatory nucleus and constitute the preganglionic elements in the parasympathetic chain to the parotid gland by way of the otic ganglion.

Vagus Nerve (X) The vagus is a mixed nerve carrying five different types of fibers. General somatic afferent fibers arise from cells in its jugular ganglion and extend peripherally to the skin in the region of the external ear. General visceral afferent fibers arise from cells in the nodose ganglion and extend peripherally to the pharynx, larynx, trachea, esophagus, and to the thoracic

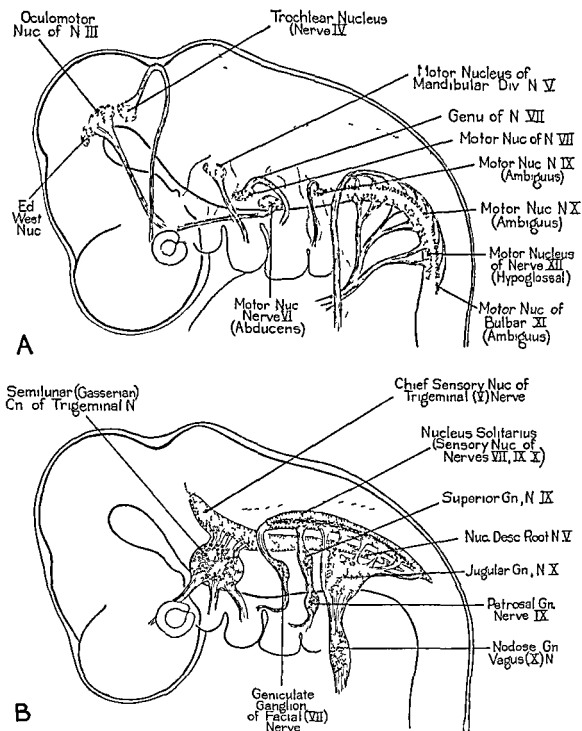


FIG 219 Relations of developing cranial nerves in a human embryo of the sixth week (Schematized from Streeter's reconstructions of a 10 mm embryo) A, Nuclei of origin of efferent components of cranial nerves B, Nuclei of termination of afferent components

Abbreviations Ed West Nuc, Edinger-Westphal nucleus, Gn, ganglion, N, nerve, Nuc Desc Root N V, nucleus of the descending or spinal root of the trigeminal nerve

and a considerable portion of the abdominal viscera. Special visceral afferent fibers having their cells of origin in the nodose ganglion carry gustatory impulses from scattered taste buds in the epithelium of the epiglottis.

From the nucleus ambiguus in the myelencephalon (Fig. 219, A), special visceral efferent fibers extend to branchiomeric muscles of the pharynx and the larynx. General visceral efferent fibers arise from the dorsal efferent nucleus (Fig. 220, C, D). This nucleus is a local specialization of the general visceral efferent column (Fig. 215) from which other cranial parasympathetic preganglionic fibers arise. These preganglionic fibers in the vagus nerve constitute the first neuron in a two-neuron parasympathetic chain supplying the thoracic, and a considerable portion of the abdominal viscera. They synapse with second-order neurons in terminal ganglia situated in or near the organ they supply.

Accessory Nerve (XI) The accessory nerve has two parts—a cranial (bulbar) portion and a spinal portion. The cranial portion is really a caudal extension of the vagus, and its fibers correspond to the general and the special visceral efferent components of the vagus nerve. The spinal portion of XI is not really a cranial nerve although its close association with the cranial portion of the accessory nerve where they leave the skull has led to their being considered together in descriptive anatomy. The cells of origin of the spinal portion of the accessory nerve lie in the ventral columns of the first five or six cervical segments of the spinal cord. The fibers emerge laterally and join each other to form an arched bundle ascending through the foramen magnum to leave the skull adjacent to the fibers of the cranial portion of the accessory nerve. They supply the sternocleidomastoid and trapezius muscles. One would regard them as special visceral efferent if one held that these muscles were of branchiomeric origin. If one believed them to be of somitic origin the nerve fibers supplying them would be regarded as general somatic efferent.

In embryos of six to eight weeks there is a strand of ganglionic cells (accessory or commissural ganglion) extending from the jugular ganglion caudally along the rootlets of the accessory nerve. The most caudal part of this ganglionic strand shows an enlargement known as Froriep's ganglion (Fig. 199). In the adult the entire ganglionic strand disappears almost completely, being represented only by variable vestiges of Froriep's ganglion, and occasional nerve cells along the course of the eleventh and twelfth nerves. The chief interest attaching to this ganglionic strand which is so well marked in the embryo is the evolutionary implication of the presence of ganglionic components in relation to the developing eleventh and twelfth nerves.

Hypoglossal Nerve (XII) The hypoglossal nerve is composed chiefly of somatic efferent fibers to the intrinsic muscles of the tongue (Fig. 215). These fibers arise from the elongated hypoglossal nucleus in the caudal part of the myelencephalon (Figs. 219, A, 220, C, D). In young embryos fibers from cells in the commissural ganglia, especially Froriep's ganglion, may be seen to join some of the rootlets of the hypoglossal nerve. Later in development these fibers largely disappear.

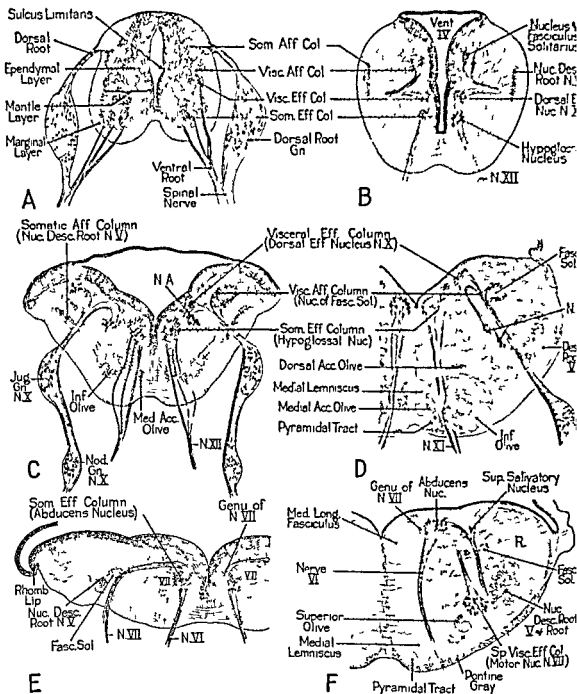


FIG 220 Cross-sections of cord and medulla comparing manner of origin of spinal and cranial nerves A, Thoracic cord of 14.8 mm embryo to show origin of typical spinal nerve B, Lower part of medulla for comparison with cord structure C, Medulla of 15 mm embryo at level of upper rootlets of nerves X and XII D, Medulla of 73 mm embryo at level of upper rootlets of nerves X and XII Compare with C E, Medulla of 15-mm embryo at level of pons showing the roots of nerves VI and VII F, Medulla of 73-mm embryo at level of pons showing the roots of nerves VI and VII Compare with E

Abbreviations Acc, accessory, Aff, afferent, Col, column, Desc, descending, Eff, efferent, Fasc Sol, fasciculus solitarius, Gn, ganglion, Inf, inferior, Jug, jugular, N A, nucleus ambiguus, note that in the younger stage (C) it is not separated from the general afferent column as happens later (D) The nucleus ambiguus, since it supplies skeletal muscle of branchiomeric origin rather than smooth muscle, is classified as a *special visceral efferent nucleus*, Nuc, nucleus, R, restiform body, Rhomb, rhombic, Sp, special, Visc, visceral

thetic chain has a retarding action. It is interesting that in this case the parasympathetic has an accelerating function, the reverse of its effect on the heart. Again in the case of the eye, the parasympathetic innervation through the ciliary ganglion causes a decrease in the size of the pupil, whereas the sympathetic innervation by way of the superior cervical ganglion produces dilation. Many other such cases could be cited but the examples given serve to illus-

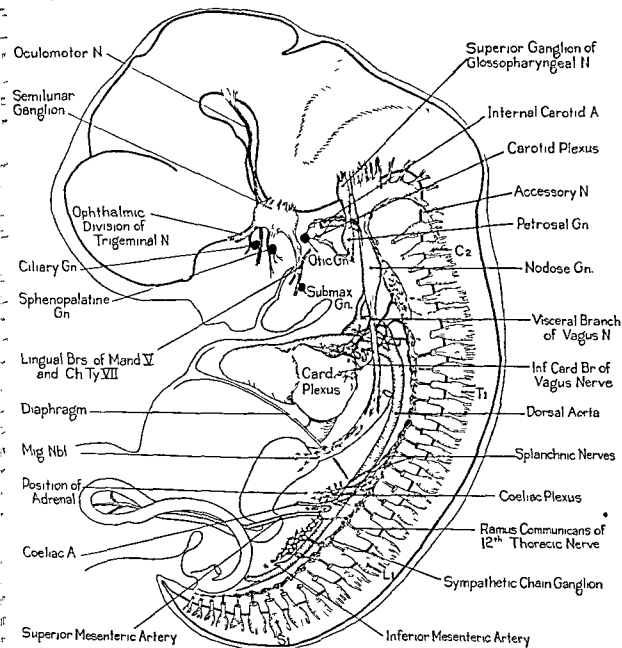


FIG 221 The autonomic nervous system of a human embryo (16 mm) of the seventh week. (After Streeter—redrawn with slight modifications)

trate the importance of the autonomic nervous system in the regulation of organ function

DEVELOPMENTAL ABNORMALITIES OF THE NERVOUS SYSTEM

Low-grade Intelligence The most serious defects of the nervous system from the standpoint of human progress are neither externally manifest nor

AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system consists of a sympathetic and a parasympathetic division. Both these divisions are composed of characteristic two-neuron efferent chains. The cell body of the first neuron in such a chain lies in the central nervous system. It is, therefore, in terms of the direction of conduction, *ahead* of a ganglion, and for this reason is commonly designated as a *preganglionic* neuron. The cell body of the second neuron in the chain is situated in a prevertebral (chain) ganglion, or in a collateral ganglion of the sympathetic division, or in a terminal ganglion of the parasympathetic division. In such a ganglion the second neuron receives impulses from the first (preganglionic) member of the chain. This second neuron which relays the impulse *beyond* the ganglion to its destination is called *postganglionic*.

The *sympathetic division* arises from the central nervous system by preganglionic neurons with cell bodies situated in the thoracic and the first three lumbar segments of the spinal cord. The postganglionic neurons of this portion of the autonomic nervous system lie in the chain and collateral ganglia (Figs. 200, 221).

The *parasympathetic division* of the autonomic nervous system has the cell bodies of its preganglionic components either in the brain or in the second to fourth sacral segments of the spinal cord. Because of the origin of their preganglionic components, the sympathetic portion of the autonomic nervous system is frequently designated as thoracolumbar, and the parasympathetic portion as craniosacral. In their peripheral distribution both these divisions of the autonomic nervous system send postganglionic fibers to practically all the viscera, and to certain structures within the head, such as the salivary gland and the ciliary muscle of the eye. There is, therefore, in these two systems with different central origins, a nearly complete overlap in distribution to internal organs. This results in the so-called double innervation of the viscera by the autonomic nervous system. This is the mechanism underlying the control of responses of alternative types. A good example of such double innervation and control is afforded by the heart. From the thoracic cord preganglionic fibers extend to the chain ganglia where they synapse with postganglionic neurons reaching the heart. Stimulation of this neuron arc causes acceleration of the heart rate. In addition to these fibers from the thoracolumbar (sympathetic) part of the system, the heart receives craniosacral (parasympathetic) innervation. This comes by way of preganglionic fibers arising from cell bodies in the medulla which send their processes peripherally through the vagus nerve to terminal ganglia on the heart, where they synapse with postganglionic neurons. Stimulation of this parasympathetic chain causes a retardation in heart rate.

The innervation of the heart outlined in the preceding paragraph is but one example of the interplay of the sympathetic and parasympathetic divisions of the autonomic nervous system which occurs in like manner in many other organs. Thus stimulation of the vagus (parasympathetic) increases peristalsis in the gastro-intestinal tract whereas stimulation of the appropriate sympa-

young nerve fibers The developing capsular connective tissue, sufficiently clearly visible in routine hematoxylin and eosin sections to suggest the adult arrangement (Fig 228, I)

in corpuscles develop in a manner much similar to that just in tile corpuscles The terminal nerve fiber of the Pacinian corpuscle some of its early branches and to form an axially located short, thorny-appearing side branches The secondary capsulation becomes much heavier and ultimately suggests the appearance of an onion (Fig 228, J-L)

and Neurotendinous Endings Closely akin to the endings of the preceding group are the neuromuscular and tendon spindles which appraise us of the position of the body and its movements Their spindles are essentially telodendria wrapped in connective tissue and secondarily encapsulated in connective tissue layers in the degree to which the muscle fibers are involved Their endings consist of telodendria which spread in the connective tissue among the tendon fibers The tendon fibers and the muscle fibers are each separately encapsulated in a common connective-tissue sheath enclosing young nerve fibers which are destined to form the neurotendinous endings can be demonstrated during their developmental period (Fig 228, N) The relation to individual muscle or tendon is shown later (Fig 228, O, P)

TASTE

What is often referred to as a general sense of our own more specialized senses of taste of course depends on materials entering the mouth and then reacting chemically with the taste buds for the differentiation of flavors only when, in evolution, the sense of smell which has developed the sense of taste of substances which elicit a response is retained from the odorous substances present in the watery solution in which the smell remains

gustatory

sensory neu-

ropharyngeal

epithelium

on the oral surface and

these cells are known as

gustatory mucosa. The chemoreceptor is a general one and the activator of the distal end of a

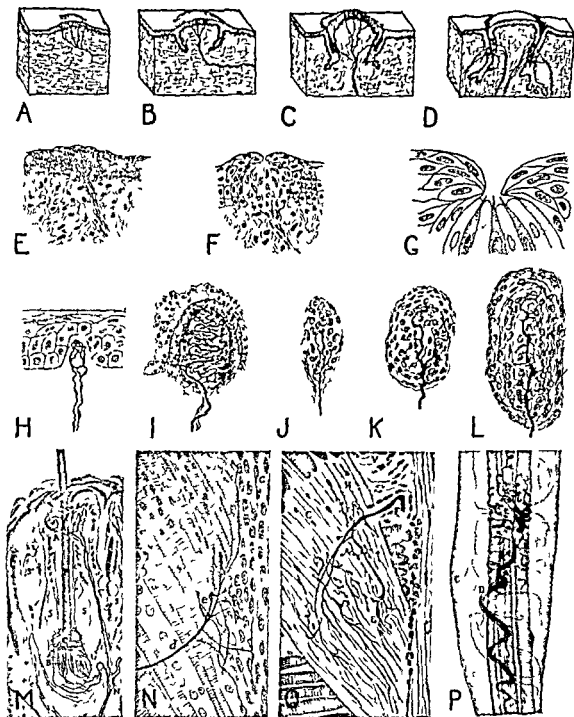


FIG 228 Stages in development of sensory nerve endings A-D, Development of circumvallate papilla (adapted from various sources especially Gräberg and Arey) E-G, Development of taste buds (after Gräberg) (E At 110 mm F at 213 mm G Pore of bud highly magnified, at 213 mm) H Nerve loops of developing Meissner corpuscle from seven month human embryo (after Tello and Arey) I, Adult Meissner corpuscle J-L, Stages in development of a Pacinian corpuscle (after Pilate in T 3 of Arch. Russe Anat. Hist. & Emb. 1925) J From skin of finger of 73 mm human embryo K, From 110 mm human embryo L From 140-mm human embryo M Developing nerve fibers around hair shaft of young mouse (Tello, 1923) Abbreviations A Superficial terminations about exit of hair B deep terminations about hair shaft C, nerve ring about hair shaft, N, nerve fibers P hair shaft S sebaceous glands N, Developing neuromuscular and neurotendinous endings from 12-day chick embryo (Tello 1917) Abbreviations a, Muscle, c tendon d, nerve fiber e nerve terminations in muscle f nerve termination in tendon O Developing neurotendinous fibers from human embryo of six months (Tello, 1917) Abbreviations C tendon fibers, F nerve fibers G, H, terminal nerve fibers I, connective tissue of blood vessel wall P Developing neuromuscular fibers from six month human embryo (Tello 1917) Abbreviations A, skeletal muscle fiber C connective tissue sheath D nerve fibers to developing spindle G, developing terminal fibers of spindle, H motor nerve fiber

strate the young nerve fibers. The developing capsular connective tissue, however, is sufficiently clearly visible in routine hematoxylin and eosin sections of older fetuses to suggest the adult arrangement (Fig. 228, I).

The Pacinian corpuscles develop in a manner much similar to that just described for tactile corpuscles. The terminal nerve fiber of the Pacinian corpuscle tends to lose some of its early branches and to form an axially located main strand with short, thorny-appearing side branches. The secondary connective-tissue encapsulation becomes much heavier and ultimately suggests the concentric layering of an onion (Fig. 228, J-L).

Neuromuscular and Neurotendinous Endings Closely akin to the sensory nerve endings of the preceding group are the neuromuscular and neurotendinous endings which appraise us of the position of the body and its parts. The neuromuscular spindles are essentially telodendria wrapped spirally around muscle fibers and secondarily encapsulated in connective tissue. They respond to changes in the degree to which the muscle fibers are stretched. The neurotendinous endings consist of telodendria which spread in a richly branching pattern among the tendon fibers. The tendon fibers and the associated nerve endings become encapsulated in a common connective-tissue investment. The richly branching young nerve fibers which are destined to give rise to neuromuscular and neurotendinous endings can be demonstrated in embryos about midway of their developmental period (Fig. 228, N), but their final characteristic course in relation to individual muscle or tendon fibers is not established until somewhat later (Fig. 228, O, P).

ORGANS OF TASTE

In primitive water-living forms there is what is often referred to as a general chemical sense which is the forerunner of our own more specialized senses of taste and smell. This general chemical sense of course depends on materials going into solution in the surrounding medium and then reacting chemically with the exposed ends of sensory cells. The basis for the differentiation of highly specialized organs of taste and smell appeared only when, in evolution, certain forms began to live in the air. Even in our sense of smell which has become a "distance receptor," appraising us of the nature of substances which may be located at a remote point, this basic method of response is retained in a slightly modified form. Air-borne particles emanating from the odorous material go into solution on our nasal mucous membranes, in the watery secretion provided by special glands. Thus in its final analysis smell remains a "solution sense."

Structural Plan of Mammalian Gustatory Organs In the gustatory organs of all the higher vertebrates the cell bodies of the primary sensory neurons lie in ganglia adjacent to the brain. In association with the peripheral dendrites of these neurons, certain cells in the oropharyngeal epithelium develop bristlelike processes projecting through the epithelial surface and acting as specialized receptors. Such modified epithelial cells are known as neuro-epithelial cells or neuromasts. The term neuromast is a general one and applies to any epithelial cell acting as an activator of the distal end of a

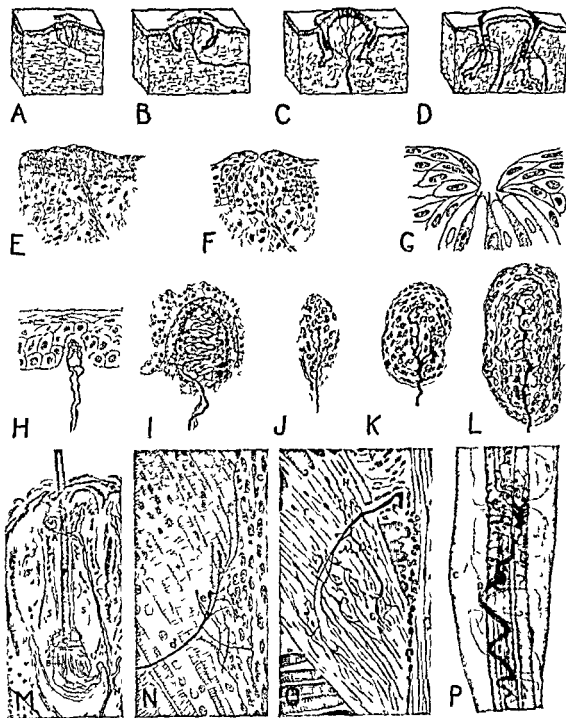


FIG. 228 Stages in development of sensory nerve endings. A-D Development of circumvallate papilla (adapted from various sources especially Gräberg and Arey) E-G Development of taste buds (after Gräberg) (E At 110 mm, F at 213 mm, G Pore of bud, highly magnified at 213 mm) H Nerve loops of developing Meissner corpuscle from seven month human embryo (after Tello and Arey) I, Adult Meissner corpuscle J-L, Stages in development of a Pacinian corpuscle (after Pilate, in T 3 of Arch. Russ. Anat. Hist. & Emb. 1925) J From skin of finger of 73 mm human embryo K From 110 mm human embryo L From 140 mm human embryo M Developing nerve fibers around hair shaft of young mouse (Tello, 1923) Abbreviations A, Superficial terminations about exit of hair B, deep terminations about hair shaft C nerve ring about hair shaft N nerve fibers P, hair shaft S sebaceous glands N Developing neuromuscular and neurotendinous endings from 12 day chick embryo (Tello, 1917) Abbreviations a, Muscle, c tendon, d, nerve fiber e nerve terminations in muscle f, nerve termination in tendon O, Developing neurotendinous fibers from human embryo of six months (Tello, 1917) Abbreviations C tendon fibers F, nerve fibers G H terminal nerve fibers, V, connective tissue of blood vessel wall P Developing neuromuscular fibers from six month human embryo (Tello, 1917) Abbreviations A skeletal muscle fiber C connective tissue sheath D, nerve fibers to developing spindle, G developing terminal fibers of spindle, H motor nerve fiber

known as the olfactory placodes (Fig 229, A) The placodes, almost as soon as they are formed, begin to sink below the general surface level so that the thickened epithelium comes to constitute the floor of the olfactory (nasal)

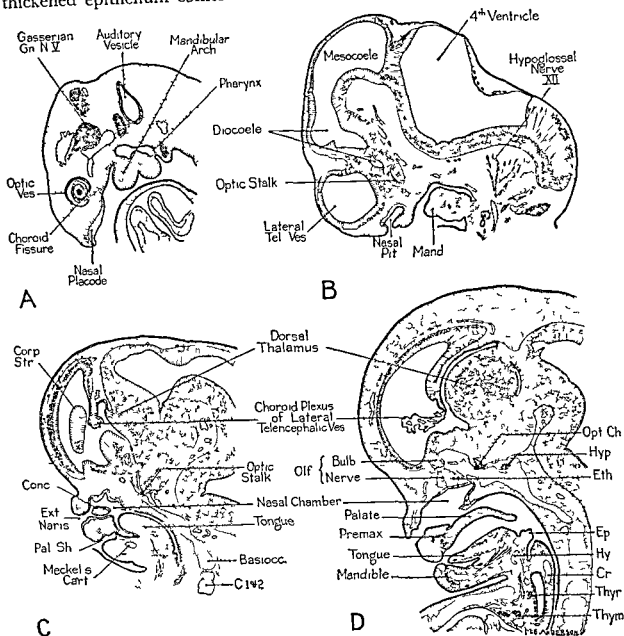


FIG 229 Parasagittal sections of young human embryos showing some of the steps in the development of the nasal chambers A, Olfactory placode at five weeks (7.5 mm) B, Blind nasal pit at six weeks (11.5 mm) C, Nasal pit shortly after it has broken through into upper part of oral cavity, during seventh week (15 mm) D, Nasal passages lengthened by formation of palate, ninth week (32 mm)

Abbreviations Conc, nasal concha, Corp Str, corpus striatum, Cr, cricoid cartilage of larynx, Ep, epiglottis, Eth, cribriform plate of ethmoid, Hy, hyoid cartilage, Hyp, hypophysis, Olf, olfactory, Opt Ch, optic chiasma, Pal Sh, palatal shelf, Thym, thymus, Thyr, thyroid

pits (Fig 229, B) Surrounding the nasal pits the mesenchymal tissue proliferates rapidly so that the pits are deepened both by their own progressive invagination, and by the forward growth of the surrounding tissue. The bordering elevations become horseshoe-shaped with their open ends toward

sensory neuron, for example, the cells in the ampullae of the semicircular canals (Fig 227, D) The deep ends of such cells are in physiological association with a basketlike arrangement of telodendria which unite in a long process leading back to the cell body of the primary sensory neuron In mammals the neuromasts concerned with the gustatory sense are grouped in small ovoid clusters with supporting cells around and between them Such a cell group is known as a taste bud (Fig 227, F) Taste buds are situated for the most part in the epithelial layer of the fungiform and circumvallate papillae of the tongue, although scattered ones occur in the pharyngeal epithelium

Development of Lingual Papillae Where a circumvallate papilla is destined to be developed the epithelium of the tongue begins, during the third month, to grow into the underlying mesenchyme in the form of a circular lamina (Fig 228, B) This originally solid epithelial lamina soon opens into a slitlike groove which circumscribes the papilla (Fig 228, C, D) and by its relations gives this particular type of lingual papilla its name The circumvallate papillae, usually 9 to 11 in number, develop along a V-shaped ridge at the boundary between the body and the root of the tongue (Fig 252) The fungiform papillae arise in a somewhat similar manner but they are smaller than the circumvallate papillae and, instead of being flat-topped and surrounded by a trench, they rise as rounded elevations above the general surface level The filiform papillae have a base still smaller than the fungiform and their top develops irregular shreds of keratinized epithelial cells

Histogenesis of Taste Buds Soon after the lingual papillae have begun to take shape, taste buds become recognizable in the epithelium of the fungiform and circumvallate types The first indication of this process is given in the fourth month by the curious pale staining reaction of a group of cells at the point where nerve fibers reach the epithelium (Fig 228, E) By the sixth month this pale staining cell group has become much more sharply delimited (Fig 228, F) and a definite pore opening on the surface is formed at its apex (Fig 228, F, G) The fully developed taste bud (Fig 227, F) shows axially a group of neuro-epithelial cells each with a slender, bristle-like process extending through the pore to the surface Encasing the neuro-epithelial cells are tall, compressed supporting cells, a few of them in between the sensory cells, but most of them arranged around the outside of the taste bud, like two or three layers of overlapping barrel staves Nerve fibers enter the base of the taste bud and break up into a basket-work around the neuro-epithelial cells These fibers are activated by physiologic changes in the neuro-epithelial cells and relay to the central nervous system the impulses initiated by the response of these receptive cells to chemical stimulation

OLFACTORY ORGAN

Development of Nasal Chambers The first indication of the formation of the nose is the appearance during the fourth week of a pair of thickened areas of ectoderm on the frontal aspect of the head These thickenings are

known as the olfactory placodes (Fig 229, A) The placodes, almost as soon as they are formed, begin to sink below the general surface level so that the thickened epithelium comes to constitute the floor of the olfactory (nasal)

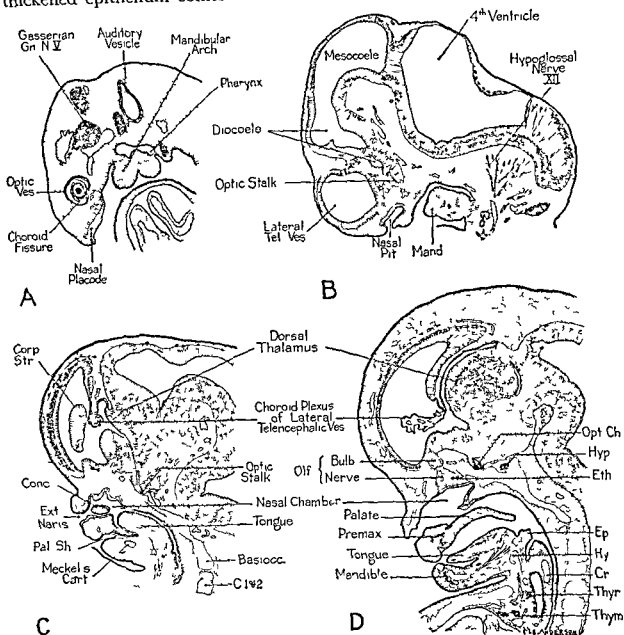


FIG 229 Parasagittal sections of young human embryos showing some of the steps in the development of the nasal chambers A, Olfactory placode at five weeks (7.5 mm) B, Blind nasal pit at six weeks (11.5 mm) C, Nasal pit shortly after it has broken through into upper part of oral cavity during seventh week (15 mm) D, Nasal passages lengthened by formation of palate, ninth week (32 mm)

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pits (Fig 229, B) Surrounding the nasal pits the mesenchymal tissue proliferates rapidly so that the pits are deepened both by their own progressive invagination, and by the forward growth of the surrounding tissue The bordering elevations become horseshoe-shaped with their open ends toward

the mouth. The two limbs of the nasal elevations are named, on the basis of their positions, the nasomedial and the nasolateral processes (Fig 247, C). At first the nasal pits are far apart, each being well to the side of the young facial region (Fig 247, B). As development progresses, the two nasal pits and their associated processes converge toward the mid-line (Fig 247, B-F). The nasomedial processes of either side eventually fuse with each other to form the medial portion of the upper lip and the septum of the nose, and the nasolateral processes become the alae of the nose.

While these changes are going on externally, the nasal pits are becoming progressively deeper and extending downward toward the oral cavity (Fig 229, B). During the seventh week the tissue separating the nasal pits from the oral cavity becomes thinned to merely a double layer of epithelium—the oro-nasal membrane. When this breaks through, as it soon does, the nasal pits open freely into the oral cavity just caudal to the arch of the upper jaw (Fig 229, C). The formation of the palate by the fusion of the palatal shelves greatly lengthens the original nasal chamber (Fig 229, D). (See also the section on the formation of the palate in the following chapter, especially Fig 250.)

Nasal Conchae In the lateral walls of the nasal chambers, elevations appear which later become converted into the scroll-like nasal conchae. The conchae are supported in young embryos by the turbinate cartilages (Fig 259) which later ossify to form the thin turbinate bones. During intra-uterine life there is a more elaborate series of conchae than in the adult, but even in his fetal stages man shows conchae which are poorly developed as compared with those mammals in which the sense of smell plays an important rôle in food getting, or in avoidance of their enemies. Of the fetal conchae (Fig 230, A) the maxillo-turbinal is the first to develop and the largest. It is converted with little change in its relations into the inferior concha of the adult (Fig 230, C). Above the maxillo-turbinal is a series of five ethmo-turbinals each one a little smaller than the one below it. The first (lowest) ethmo-turbinal forms the middle concha, and the second and third merge to form the superior concha. Ordinarily, the uppermost ethmo-turbinals in man undergo regression but occasionally they give rise to a concha suprema. A small elevation rostral to the ethmo-turbinals, known as the naso-turbinal, forms in the adult the inconspicuous rounded elevation called the agger nasi. (Cf Fig 230, A, C.)

Olfactory Area The epithelium lining the nasal chamber is at first of the simple cuboidal to columnar type, like almost all the epithelial layers in a young embryo. It gradually becomes transformed through most of its extent into a pseudostratified to stratified columnar ciliated epithelium with many goblet cells. The middle of the roof of each nasal chamber and the lining for a distance of 8–10 mm. onto the septum medially and about the same distance onto the superior concha laterally constitute the olfactory area. In this area goblet cells are absent and the tall columnar cells of the layer lack cilia and serve as supporting cells. The cells which are destined to act as olfactory receptors develop bristlelike processes distally which project through the

epithelial surface. Centrally they form a nonmedullated axonic process which makes synapse with the mitral cells in the olfactory bulb (Fig 227, E). The mitral cells in turn relay the olfactory impulses over the olfactory tract to the appropriate centers in the central nervous system.

Paranasal Sinuses Connecting with the nasal cavities are a number of chambers in the bones of the skull. These irregularly shaped spaces lined by

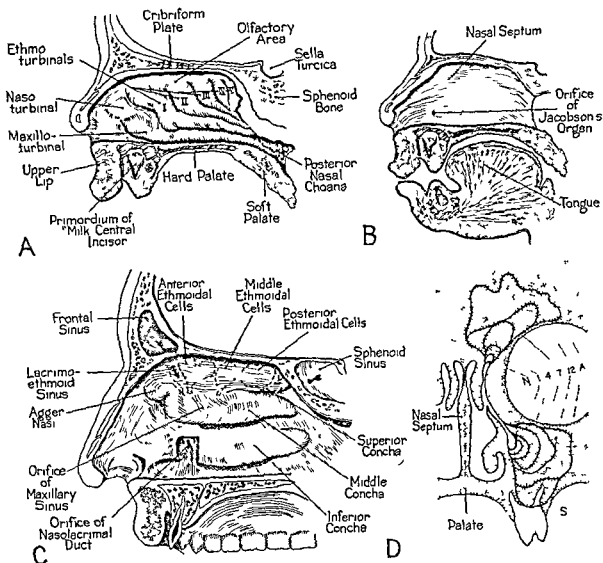


FIG 230 Development of nasal conchae and paranasal sinuses (Adapted from a number of sources, chiefly Kullian, Arcy, and Torrigiani.) A, Lateral wall of fetal nose to show turbinals. B, Medial wall of fetal nose showing location of Jacobson's organ. C, Lateral wall of adult nose to show relations of conchae and paranasal sinuses. D, Schematic frontal section of one side of head to show postnatal growth of paranasal sinuses. A = adult, N = newborn, S = senile. The numbers indicate ages in years.

extensions of the nasal mucosa are known as the paranasal sinuses. They are named on the basis of the bone in which their cavity is located and include the irregular group of ethmoid cells, the frontal sinuses, the maxillary sinuses, and the sphenoid sinuses (Fig 230, C). Except for the sphenoid sinuses, which are not formed until after birth, these sinuses make their first appearance during the fourth or early in the fifth month of fetal life. In their formation

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Other basic facts to have clearly in mind at the outset concern the different sources from which various parts of the complex visual organ derive their primordia. The retina, as has just been emphasized, arises as a segregation and specialization of a portion of the brain wall, but the crystalline lens which brings the light rays to proper focus on the photoreceptive cells of the retina is developed from a secondary ingrowth of the superficial ectoderm. The supporting investment of tough connective tissue, called the sclera, which gives the eyeball its shape and, by acting against internal fluid pressure, permits it to develop the necessary firmness, arises from a concentration of mesenchymal cells about the optic cup. The eyelids are formed from folds of skin after most of the other parts of the eye have been established. The special groups of muscles which move the eyeballs are molded from concentrations of mesodermal cells which are believed to stem, phylogenetically, from primitive head somites no longer identifiable as such in mammalian embryos. The fact that there are so many growth processes which start more or less independently and then become co-ordinated determines the plan which must be followed in the presentation of eye development. The early differentiation of each of the component parts must first be followed to a point where it is ready to fall into its place in the general organization. Not before this groundwork has been laid can one logically discuss the later changes in any of the regions where these parts are becoming interrelated.

Primary Optic Vesicle. In human embryos the evagination of the optic vesicles begins very early. By the middle of the third week (embryos of 7 to 9 somites) depressions appear in the still open neural plate where it widens out in the future forebrain region. These early depressions are called the *optic sulci* (Fig. 49, B). They are the initial shallow concavities that later become deepened to form the optic vesicles.¹ After the neural plate in the brain region has been closed, the optic vesicles appear in external views of reconstructions of the central nervous system as rounded protuberances from the lateral walls of the forebrain (Fig. 66, A).

Formation of Optic Cup from Primary Optic Vesicle. In an embryo toward the end of the fourth week, the lumen of the primary optic vesicle is still broadly continuous with the lumen of the forebrain, and the walls of the vesicles show little differentiation from the condition of the parent forebrain walls (Fig. 231, B). At the start of the fifth week, the distal portion of the optic vesicle begins to flatten (Fig. 231, C) and very soon thereafter to become invaginated so that the single-walled primary vesicle becomes transformed into the double-walled optic cup (Fig. 231, D). As the invagination becomes more complete, the original lumen of the optic vesicle is reduced to a vestigial slit between the inner and outer layers of the newly formed cup (Fig. 231, C-F). At the same time there is rapid differentiation of the two layers of the cup.

¹ Cf. Fig. 231, A, B. "A" is a section passing through the optic sulci of the 14 somite embryo shown in Fig. 50, B. The section is at the level of the leader from "margin of neural folds." "B" is a section of the left optic vesicle in an embryo shortly after the forebrain has become closed. It was taken from a specimen almost exactly the same size as that shown in Fig. 53.

there is an invasion of the bone by an outgrowth of the nasal mucosa, and the excavation of the bone to form the expanding sinus seems to be in some way activated by these mucosal outgrowths. All the sinuses are still very small at the time of birth and indeed do not attain their full size until many years later. An indication of the rate of their expansion is given graphically in Fig 230, D.

Abnormalities of the Nose Disturbances involving the failure of the nasal pits to develop normally seem to have a curious sequel in the way the tissue constituting the nasal processes grows. There is a strong tendency for the nasal processes in such cases to develop into cylindrical masses of soft tissue projecting—proboscis-like—from the face. The “proboscis” may represent both halves of the nose fused with each other into a single median structure (Fig 255, D), or each nostril may be represented by a separate roll of flesh. Sometimes when they are thus separate, these curious structures are carried to bizarre asymmetrical locations (Fig 255, F). Ordinarily in such malformations there is little more than a surface dimple indicating where the nostril should have been.

Among the exceedingly rare anomalies of the face is a condition in which the two halves of the nose remain in their primitive lateral locations without converging to meet each other in the mid-line. Such a defect is usually combined with other disturbances of growth in the median portion of the head (Fig 255, A). There are, however, a few cases on record in which the separation of the two halves of the nose is the only conspicuous malformation.

There is a considerable period during development when the external nares are normally occluded by a solid mass of epithelium. In occasional cases these epithelial plugs fail to regress, with a resultant atresia of the nasal openings (Fig 255, C).

By all odds the commonest developmental defect affecting the nasal region is the failure to form a proper floor of the nasal chambers which occurs in cases of cleft lip and cleft palate. This condition is discussed in the next chapter in connection with the development of the oral region.

THE EYE

The study of young embryos has already made us familiar with the general nature of the processes involved in the establishing of the primary optic primordia. Certain points should, however, be emphasized again at the outset of this section on the later development of the eye. Probably most important among them is the fact that from a developmental standpoint the eye is radically different from other general or special sense organs in that its receptive area, the retina, is in reality part of the wall of the brain carried out first as a vesicle (Fig 231, A, B), and then converted into a cup (Fig 231, D, E) with the lining of the cup containing the cells which are specialized to form the light-sensitive elements. This manner of origin carries as a corollary the fact that what in descriptive anatomy is called optic nerve is in reality not a typical nerve but a fiber tract which develops along a stalk of brain tissue.

The outer layer becomes much thinner, and by the sixth week begins to show melanin granules which foreshadow its ultimate conversion into the pigment layer of the retina. The inner layer of the cup becomes much thickened, indicative of its start on the elaborate series of changes by which it will become the sensory layer of the retina.

The invagination which forms the optic cup does not occur at the center of the optic vesicle, but eccentrically, toward its ventral margin. This makes a gap in the continuity of the wall of the optic cup which is known as the *choroid fissure*. This fissure is most clearly seen in parasagittal sections of the head that cut through the rim of the optic cup (Fig 229, A). In reading transverse serial sections the ventral lip of the cup will seem suddenly to drop out as the plane of sectioning comes into the fissure. Sections which do not pass quite symmetrically across the head frequently show an apparently complete optic cup on one side, and one without a ventral lip on the other side where the plane of sectioning coincides with the choroid fissure (Fig 55, B). The gap in the ventral side of the optic cup is carried back onto the optic stalk as a groove (Figs 235, A, 237, A). As we shall see later, it is through this opening in the walls of the cup, and along the groove in the optic stalk, that the optic nerve grows.

Establishing of the Lens While these changes have been going on in the optic cup, the primordium of the lens is laid down. At about the end of the fourth or the beginning of the fifth week (embryos of 4 to 5 mm) the superficial ectoderm immediately overlying the optic cup begins to develop a local thickening known as the lens placode (Fig 231, C). As the cavity in the optic cup deepens, the lens placode becomes invaginated into the cup to form an open lens vesicle, sometimes called the lens pit (Fig 231, D). During the fifth week, the lens vesicle becomes closed (Fig 231, E) and then breaks away completely from the parent ectoderm to constitute a rounded epithelial body lying in the opening of the optic cup (Fig 231, F). Before the end of the sixth week, the cells on the deep pole of the lens are beginning to elongate, presaging their transformation into the long transparent elements known as lens fibers (Fig 231, F).

Later Development of the Lens The cells that form the front surface of the lens do not show the tendency to elongate exhibited by the cells on the deep surface. They constitute a cuboidal to low columnar layer known as the lens epithelium (Fig 232, A). By the end of the seventh week (embryos of 17 to 20 mm), the lens fibers have elongated sufficiently to make contact with the lens epithelium, thus reducing the original cavity in the lens vesicle to a potential slit. In the living condition and in undistorted preparations the two layers are in contact but the shrinkage involved in fixation usually opens the slit to varying degrees.

The formation of lens fibers by no means ceases when the lens has become thus solid. This forms but the core of the lens, about which new fibers continue to be added throughout fetal life and into the postnatal period. The new lens fibers arise from cells proliferated in an equatorial zone about the lens

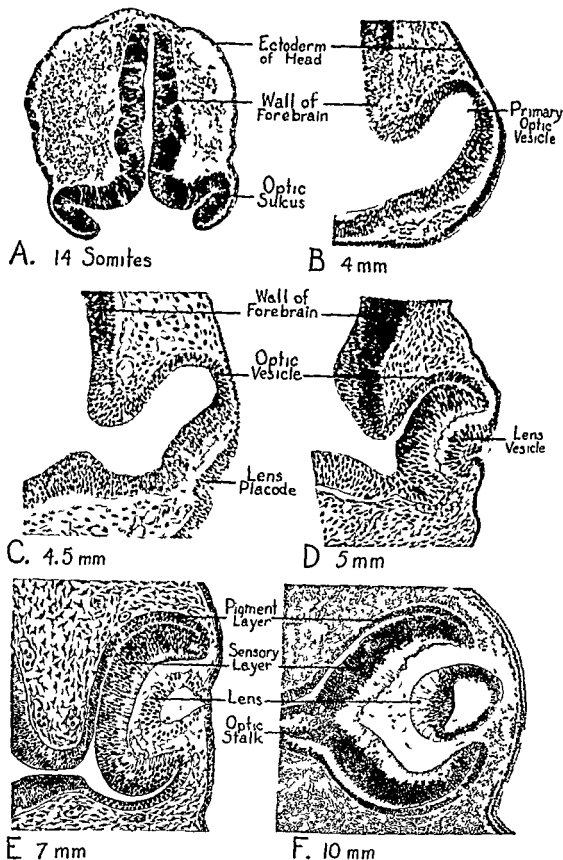


FIG 231 Early development of optic cup and lens. Photomicrographs and drawings from various sources placed in corresponding orientation and brought to same magnification ($\times 100$). A, From Heuser B, From Fischel C, D, E, From Ida Mann F, From Prentiss

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which is clearly marked by the abundance of the nuclei there appearing (Fig 232, C) The tips of these new lens fibers grow toward the external and internal poles of the lens Thus at each pole of the lens there is a place where

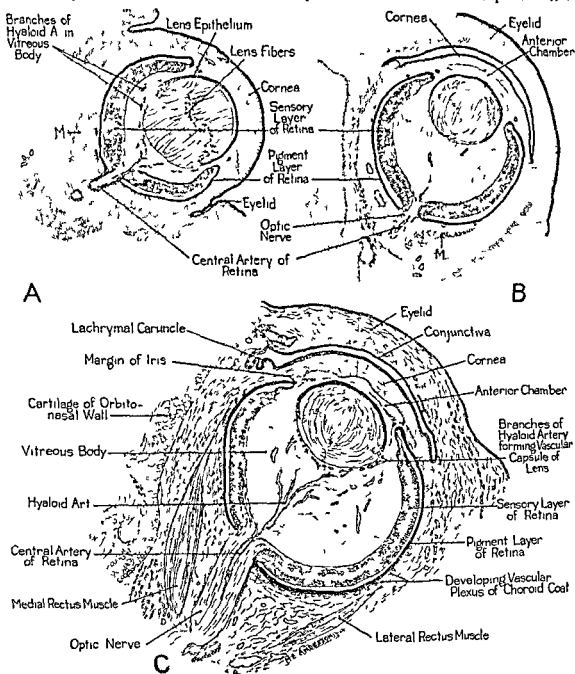


FIG 232 Three stages in development of the eye as seen in coronal sections of the head A, From an embryo of 17 mm, about seven weeks (Projection drawing, $\times 50$, from University of Michigan Coll, EH 14) B, From an embryo of 33 mm, about middle of ninth week (Projection drawing, $\times 35$, from University of Michigan Coll, EH 217) C, From an embryo of 48 mm, about middle of tenth week (Adapted from Ida Mann, $\times 25$)

Abbreviation M, primordial mesenchymal concentration for eye muscle

fibers arising at opposite points on the equator meet each other Each lens fiber extends all the way from one pole of the lens to the other so that as the lens grows the fibers become progressively greater in length There is,

however, a tendency for the fibers to be just a shade shorter than they would have to be to go from the exact center of one face of the lens to the exact center of its other face. As a result the place of meeting of the fibers on the two poles forms an irregular pattern known as the lines of lens fiber sutures, or simply lens sutures (Fig. 233). New lens fibers continue to be added until about the twentieth year. According to Arcey their total number is fairly constant, approximating 2250.

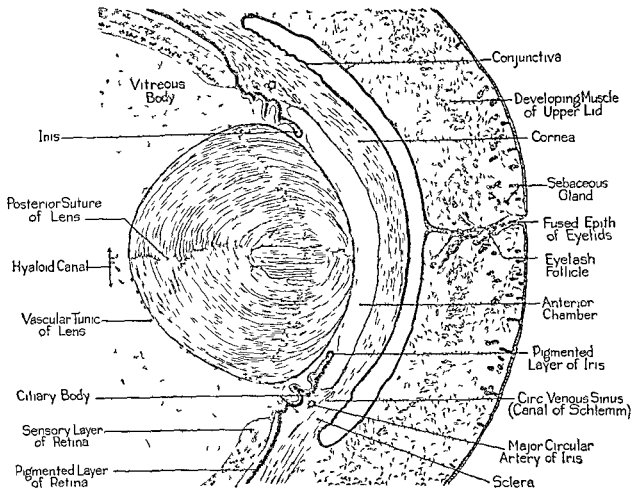


FIG. 233 Anterior part of the eye from a fetus of about 19 weeks (174 mm.) Vertical section ($\times 20$) to show fused eyelids, developing ciliary region, and lens.

Iris and Ciliary Apparatus As the lens increases in size, it settles back into the optic cup and the margins of the cup begin to overlap its edges. We can now recognize the thin overlapping part of the optic cup as the epithelial portion of the iris and the reduced opening in front of the lens as the pupil. The retina may now be divided into two portions, the back two-thirds which is specialized in photoreception and constitutes the *pars optica retinae*, and the front margins constituting the *pars caeca retinae* (Latin, caecus = blind). The line of demarcation between these two parts is a wavy circle, the *ora serrata*. The blind portion of the retina may be subdivided into the *pars iridica retinae* and the *pars ciliaris retinae*. These parts of the optic cup remain as a double

layer of epithelium. In young embryos only the outer of these epithelial layers is pigmented, but during the latter part of fetal life the inner layer also becomes pigmented.

In embryos of the fifth month (Fig. 233) a delicate layer of mesenchymal tissue can be seen adherent to the outer of the two epithelial layers which constitute the pars iridica retinae. In the fetal eye this layer extends beyond the margin of the iris and across the front of the lens as the so-called pupillary membrane. Over the lens this membrane is resorbed in the last months before birth, thus clearing the pupil. Considerable mesenchymal tissue persists over the pars iridica retinae, and between it and the epithelium smooth muscle elements make their appearance. According to a number of authorities this smooth muscle of the iris is peculiar in arising from the ectodermal epithelial layer of the iris rather than from the closely associated overlying mesenchymal layer. The characteristic arrangement of this muscle of the iris in two groups of fibers, a circular band, and radially arranged bundles, obviously provides for control of the size of the pupil.

As is the case with the iris, part of the adult ciliary body is derived from mesenchymal cells which concentrate about this zone of the optic cup. In fetuses of the fifth month (Fig. 233), the pars ciliaris retinae is readily identifiable by the marked folding which has involved this portion of the original optic cup. The folding foreshadows the formation of the radially arranged ciliary processes. Outside the epithelial layer may be seen the loosely aggregated mesenchyme which will be organized into the muscular portion of the ciliary body. This ciliary muscle, by altering the tension on the suspensory ligament of the lens, controls the lens curvature and thereby permits the eye to change focus so objects at different distances can be made to cast sharp images on the retina.

Choroid Coat and Sclera Outside the optic cup, mesenchymal cells early become massed in a concentrated zone. As development progresses this mesenchymal coat becomes differentiated into an inner, highly vascular tunic known as the choroid coat (Figs. 232, C, 237, D), and an outer tunic composed of densely woven fibrous connective tissue known as the scleroid coat or sclera. The tough sclera molds the eyeball and gives firm attachment to the muscles which move the eye in its socket. Centrally the sclera is continuous with the dura mater by way of the sheath of the optic nerve.

Cornea Continuous with the sclera in front, and forming the part of the eye overlying the lens and the iris, is the cornea. The outermost layer of the cornea is an epithelium, derived from the superficial ectoderm where it closed over the lens vesicle (Figs. 231, 232). The main mass of the cornea is a dense fibrous layer called the substantia propria. This has the same mesenchymal origin as the sclera, but the cornea, like the lens, is modified so that its fibers become transparent. Its curvature is on a smaller radius than that of the remainder of the eyeball and in consequence the cornea appears to bulge out from the eye as a whole. The perfection of this corneal curvature is of great functional importance, for the cornea is what we might call the front lens of

the eye and acts in conjunction with the crystalline lens in bringing light rays into focus on the retina

Anterior and Posterior Chambers As the mesenchymal tissue condenses and differentiates to form the cornea the cells rearrange themselves in such a manner that a space is formed beneath the cornea and outside the lens. This space is known as the anterior chamber (Fig 232, B, C) and comes to be lined with flattened mesenchymal cells, which on the back face of the cornea constitute the posterior corneal epithelium (corneal endothelium). This layer is recurved over the iris, and in the middle trimester of fetal life extends also across the pupil as part of the pupillary membrane. During this period delicate vascular loops extend radially from the iris into the pupillary membrane.

The space just behind the iris, in the angle between it and the lens and suspensory ligament, is known as the posterior chamber. In the fetus the anterior and posterior chambers are separated from each other by the pupillary membrane until about the seventh month. At this time resorption of the membrane and its vascular loops begins and is usually pretty well completed during the eighth month, although traces in the form of delicate fibrous filaments may persist even at term. The disappearance of the pupillary membrane places the anterior and posterior chambers in communication by way of the narrow space between the margins of the iris and the lens. These chambers become filled with a clear watery fluid known as the *aqueous humor*.

Vitreous Body It will be recalled that in embryos of the fifth and sixth weeks the optic cup shows a gap at the choroid fissure. During this early period, mesenchymal cells enter the cup through the choroid fissure and also between the margins of the cup and the lens. Apparently most of these mesenchymal cells within the optic cup are involved in the formation of the blood vessels and their associated connective tissue. The space between the vessels and the walls of the optic cup is filled with a delicate meshwork of fibers which have very few cells associated with them (Fig 232). Most recent observers feel that these fibers are derived from the cells lining the optic cup and possibly also in very early stages from the back of the young lens vesicle. This ectodermal origin and their general configuration would place them in the same general category as neuroglial fibers—a conclusion not illogical in view of the previously emphasized fact that the optic cup is in reality a portion of the wall of the embryonic forebrain. There is direct continuity of these fibers with the connective tissue around the hyaloid vessels and it is possible that in later stages the original fibers are added to by the activity of the cells in this connective tissue of the usual mesenchymal origin. The interstitial spaces among both primary and secondary fibers become filled with a gelatinous material of glasslike transparency. The fibers themselves become transparent and together with the material in their meshes constitute the vitreous body.

Histogenesis of Retina The part of the primary optic vesicle that is destined to form the light-sensitive area of the retina (*pars optica retinae*) is at first fairly uniformly nucleated throughout its thickness (Fig 231, B). By the fifth week the first of a series of shifts in nuclear arrangement occurs with

the resultant formation of an inner layer devoid of nuclei, and an outer² nuclear layer (Fig 231, C, D) The inner layer corresponds with the marginal layer of the brain wall, and the outer nuclear layer corresponds with the mantle layer and like it contains both young neuroblasts and spongioblasts. About the middle of the sixth week a few of the cells composing the original outer nuclear layer begin to migrate centrally (Fig 231, I) This migration, starting first near the center of the cup, spreads rapidly until by the end of the seventh week there is a definite inner cellular zone established, which is known as the inner neuroblastic layer. As a result of the way it originates the inner neuroblastic layer is separated by a narrow anuclear zone (the transient layer of Chievitz) from the cells which remain in their original position and now may be said to constitute the outer neuroblastic layer (Fig 234, A)

Toward the close of the third month certain conspicuously large cells in the inner neuroblastic layer have begun to move still farther inward so that they form a new, separate layer. These are the ganglion cells which are already sending long axonic processes over the inner surface of the retina (Fig 234, B, C) These fibers as they converge from their points of origin toward the optic stalk constitute a fibrous layer within the ganglion cell layer. At the point of continuity with the optic stalk these fibers leave the eyeball and course together along the optic stalk to form the optic nerve.

The migration of additional cells from the outer, toward the inner, neuroblastic layer gradually obliterates the transient layer of Chievitz (Cf Fig 234, A, with B, C, see table, third stage) When this has occurred, one can recognize three quite definite nuclear zones separated from one another by zones of delicate fibrillar character. From within outward these nuclear zones are the ganglion cell layer, the inner nuclear layer, and the outer nuclear layer (Fig 234, C) By looking at a diagram showing the arrangement of elements in the adult retina (Fig 234, E) we can see the nature of the specialized structures the primordia for which are being segregated in these layers. The significance of the large cells in the ganglion cell layer as conducting elements has just been pointed out. The majority of the cells in the inner nuclear layer give rise to the bipolar neurons which relay impulses from the rods and cones to the ganglion cells. In this layer also are the nuclei of spindle-shaped supporting cells of neuroglial type (Muller's cells), and cells which send processes horizontally, interconnecting groups of photosensitive cells (Fig 234, E) The nuclei in the outer layer are primarily the nuclei of the two types of photoreceptors—the rods and the cones—which are very late in completing their differentiation. For the details of their histogenesis, reference should be made to the exceptionally complete account in Ida Mann's "The Development of the Human Eye."

The accompanying table taken from Mann's account summarizes the

² The terms inner and outer as commonly used describing structures in the eye refer to the topography of the eyeball itself rather than to the relations of the structures in the head. Thus the "inner" layer of the optic cup is the layer toward the center of the cup, not the layer toward the brain.

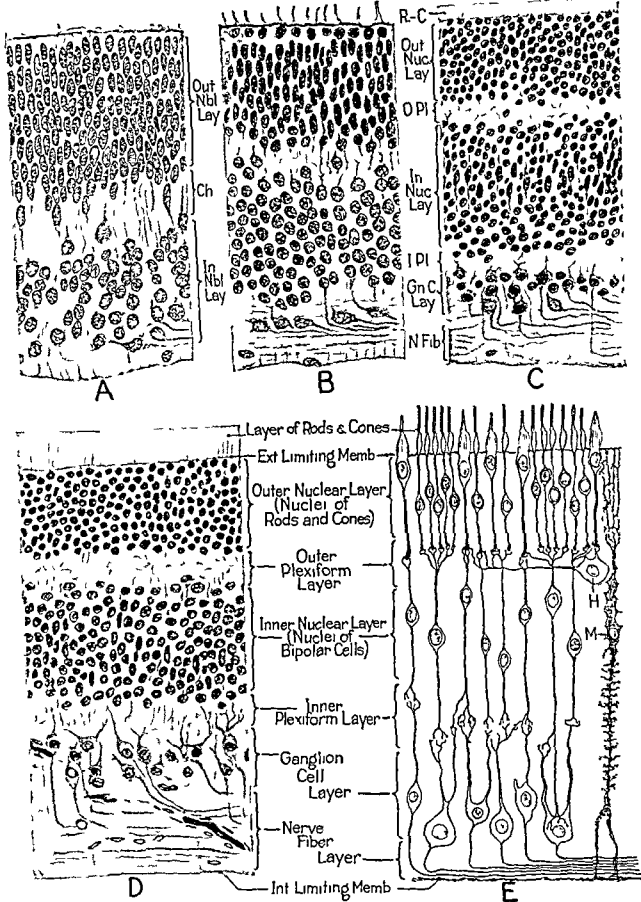
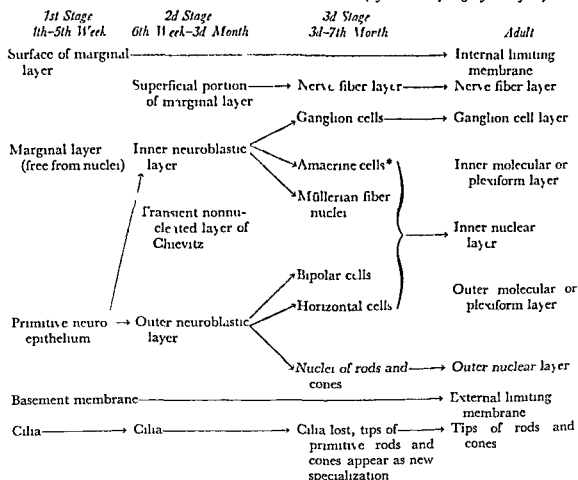


FIG 234 Stages in histogenesis of retina (A-D, redrawn, $\times 500$, from Ida Mann) A, From embryo of about seven weeks (17 mm) B, From fetus of about 11 weeks (65 mm) C, From fetus of about 19 weeks (170 mm) D, From fetus of twenty-seventh week (250 mm) E, Schematic plan to show relations of various elements of retina

Abbreviations Ch, transient fiber layer of Chievitz, Gn C Lay, ganglion cell layer, H, horizontal cell, In Nbl Lay, inner neuroblastic layer, In Nuc Lay, inner nuclear layer, I Pl, inner plexiform layer, M, Muller's cell, N Fib, layer of nerve fibers, O Pl, outer plexiform layer, Out Nbl Lay, outer neuroblastic layer, Out Nuc Lay, outer nuclear layer. R-C, layer of rods

main steps by which the characteristic layers of the adult retina are formed by rearrangements and specializations of the inner and outer neuroblastic layers. As emphasized by Mann, this differentiation progresses in inverse sequence to the direction in which the nerve impulses are destined to pass. That is to say, the ganglion cells and the nerve fibers arising from them and extending to the visual centers in the brain are differentiated first, and the light-sensitive cells—the rods and cones—are the last to acquire their definitive form. This means that when the photoreceptive elements are ready to function, the transmitting elements are already established and the entire intricate mechanism is ready to go into immediate operation.

TABLE SUMMARIZING THE REORGANIZATION OF THE PRIMITIVE EMBRYONIC LAYERS INVOLVED IN THE HISTOGENESIS OF THE RETINA (*after Mann, slightly modified*)



* The connections and functional significance of the amacrine cells being uncertain, they were omitted from the diagram of Fig. 234 E.

Outside the sensory layer of the retina, but intimately adherent to it, is the pigment layer. This is the original outer layer of the double-walled optic cup (Figs. 231, 232). Its cells develop processes about the tips of the rods and cones. The migration of pigment granules into these processes partially screens the photosensitive elements when the light is brilliant. When the light is dim the pigment moves away from the tips of the rods and cones, thus permitting all the available light to fall on them. The length of time this pigment migra-

tion takes is an important factor in the time it takes one's eyes to "become adapted" to a dimly lit room after having been in bright sunlight

Formation of Optic Nerve Attention has previously been called to the fact that the young optic cup shows a gap in its walls, known as the choroid fissure (Fig 229, A) This fissure in the cup is continued as a groove along the ventral surface of the optic stalk (Figs 235, A, 237, A) By way of this groove

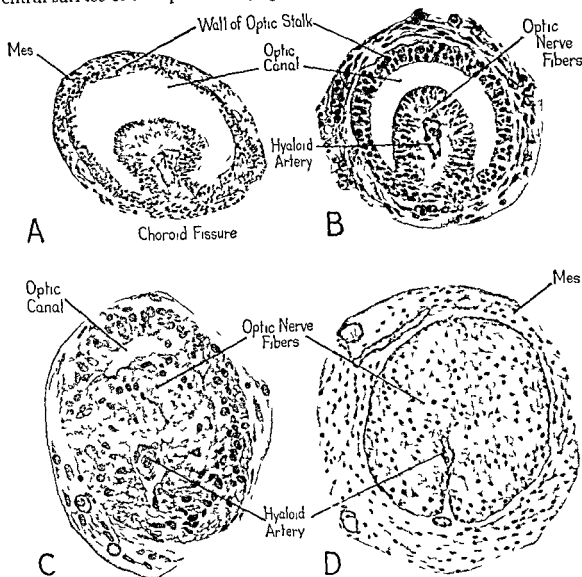


FIG 235 The changes in the optic stalk and the development of optic nerve fibers in human embryos A, At 9 mm (sixth week) (after Fischel) B, At 14.5 mm (early in seventh week) (after Bach and Seefelder) C, At 19 mm (end of seventh week) (after Bach and Seefelder) D, At 25 mm (late in eighth week) (after Ida Mann)

in the stalk, and through the choroid fissure, the ophthalmic artery sends a branch into the optic cup. In the embryo this entire vessel is often called the hyaloid artery (Fig 235) because its direct continuations as the hyaloid arteries to the lens (Fig 237, C) are at first its only main branches. Because the hyaloid branches degenerate and new branches develop supplying the retina, the proximal part of this artery is known in the adult as the central artery of the retina. Having in mind this ultimate fate, many people prefer

to call the part of the artery in the optic stalk by its adult name even before it has developed its characteristic branches to the retina. When the choroid fissure closes, the presence of this vessel and its associated connective tissue keeps open a pathway in the optic stalk. Coincidentally, the nerve fibers arising from the ganglion cells in the retina grow along the marginal layer, close to the vessels which lie inside the double-walled epithelial tube formed from the optic stalk when, toward the close of the sixth or beginning of the seventh week, the choroid groove closes (Fig 235, B). As more and more fibers traverse the stalk, they begin to be crowded progressively deeper in the reticulated cytoplasm of its cells (Fig 235, C). The original lumen of the stalk (optic canal) becomes progressively smaller, and finally disappears completely. At the same time the cells of the stalk, having served as a pathway for the growing optic fibers, begin to undergo regression. This leaves the proximal part of the hyaloid artery (central artery of the retina) embedded in the optic nerve fibers (Fig 235). When these fibers become medullated and the nerve as a whole acquires a well-developed connective-tissue sheath there is little left of the original tissue of the optic stalk except some 'glialike supporting elements.

Optic Pathways to Visual Centers The optic nerves of the two eyes converge to form the chiasma at the base of the diencephalon just rostral to the hypophyseal stalk. In the optic chiasma the fibers from the nasal half of each retina cross to the opposite side and pass by way of the optic tract to the lateral geniculate nucleus. The fibers from the temporal half of each retina pass back to the optic tracts and lateral geniculate bodies without crossing in the chiasma (Fig 236). Neurons of the lateral geniculate nucleus relay the incoming impulses by way of the optic radiations to the visual projection centers of the cortex. These centers are located in the occipital lobe along the superior and inferior lips of the calcarine fissure.

In their transmission from retina to cortex the impulses from specific portions of the retina are projected on specific parts of the cortex. This is made possible by a definite pattern in the arrangement of the fiber tracts and of the relaying cells in the lateral geniculate nuclei. No attempt has been made in Fig 236 to show all the details of this complicated pattern. The illustration does, however, indicate the projection from the retinal elements in the upper part of the retina onto the superior lip of the calcarine fissure, and from the inferior half of the retina onto the inferior lip. It is the existence of patterns of this sort which accounts for such clinical findings as the fact that a hemorrhage in the superior lips of the calcarine fissures interrupts visual projection from the superior parts of each retina. With the inversion due to the camerallike action of the cornea and lens, this would mean blindness to things in the lower part of the visual field.

Blood Vessels of the Eye The entry of the primary arterial branch from the ophthalmic artery into the optic cup was just discussed in connection with the development of the optic nerve. In young embryos the vessel supplies by its hyaloid branches primarily the vitreous body and the lens (Fig 237, C). Only relatively late in development do the retinal branches radiate out

from its point of entry to be distributed over the inner surface of the retina (Fig 237, D)

As the secondary mesodermal coats of the eye are formed, three sets of small arteries arise from the main ophthalmic artery, and enter the outer

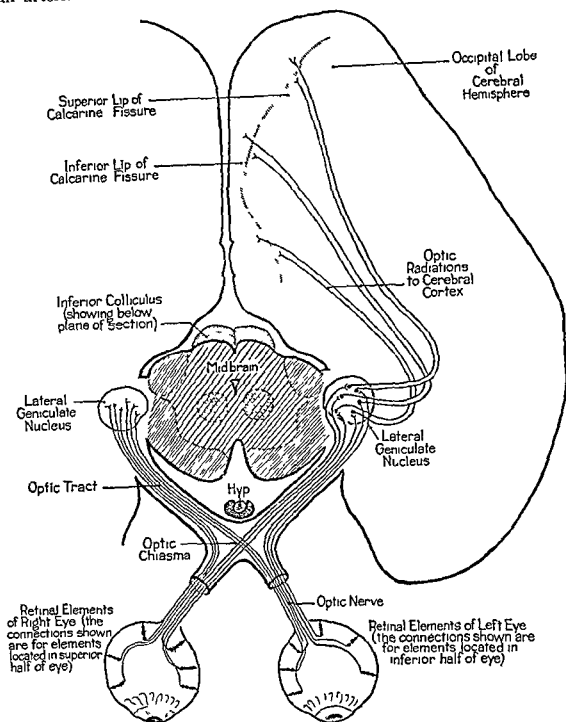


FIG 236 Optic pathways to visual centers of the brain (Drawn with the collaboration of Dr Elizabeth C Crosby)

coats of the eye These arteries are the short posterior ciliaries, the long posterior ciliaries, and the anterior ciliaries (Fig 237, D) The short posterior ciliary arteries—usually five or six in number—penetrate the back of the eyeball and break up in the rich vascular plexus of the choroid coat The long posterior ciliary arteries—usually two in number—anastomose with the

anterior ciliary arteries to supply the ciliary body and the iris. The feeder channel for the arterioles which radiate into the iris and the ciliary body is an annular vessel known as the major circular artery of the iris (Fig 233)

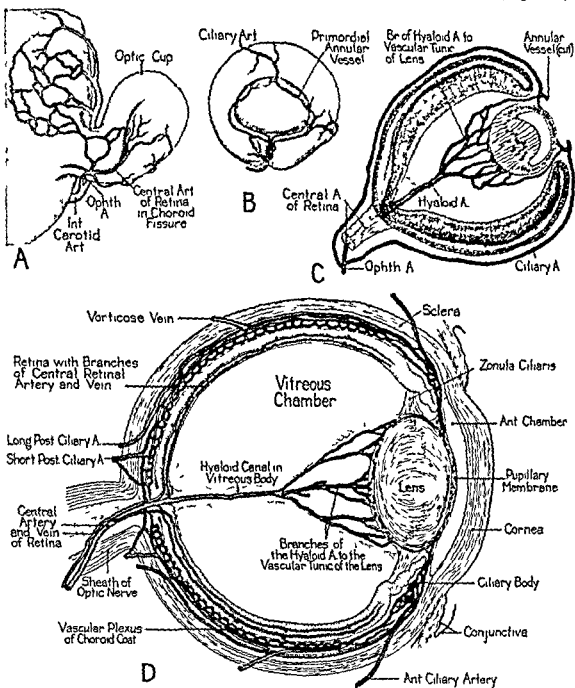


FIG 237 Stages in development of blood vessels of the eye (A-C adapted from Ida Mann, D from Corning) A, Left optic cup of a 5-mm embryo viewed from in front and below B, Optic cup and lens of a 10 mm embryo viewed from the side C, Sectional diagram of optic cup and lens of a 13 mm embryo D, Schematic plan of circulation in the fetal eye before the degeneration of the hyaloid vessels and the vascular tunic of the lens

The start of this vessel is recognizable around the margin of the optic cup at a surprisingly early stage (Fig 237, B)

The drainage of the eye involves both the return of the blood brought in

by the arteries and the taking away of the proper amount of fluid from within the eyeball so that intra-ocular pressure is maintained within normal levels. The retina is drained by veins paralleling the arterial vessels which supply the retina (Fig 237, D). The iris and ciliary body are drained by small channels many of which enter an annular venous channel inappropriately known as the canal of Schlemm (Fig 233). It is believed to be the percolation of fluid from the angle of the anterior chamber by way of coarse interstices (spaces of Fontana) in the underlying connective tissue into the canal of Schlemm that takes off the excess fluid from within the eyeball along with the venous blood. For this reason the recess of the anterior chamber where the endothelial lining turns from the front of the iris to the back of the cornea is spoken of as the "filtration angle." From the canal of Schlemm and from numerous small venous channels in the choroid coat most of the blood which was brought to the outer layers of the eye by the choroid arteries leaves the eye by way of the vorticosae veins. The vorticosae veins discharge through the posterior ciliary veins and the superior ophthalmic veins into the cavernous sinus.

Eyelids, Conjunctiva, and Associated Glands The eyelids start to develop during the seventh week as folds of skin growing back over the cornea (Figs 62, 232, A). Once having started to form they close over the eye quite rapidly, usually meeting and fusing with each other by the end of the ninth week (Fig 109, A, B). This fusion involves only the epithelial layers of the lids (Fig 233) and the eyelashes and the glands that lie along the margins of the lids start to differentiate from this common epithelial lamina before the lids reopen. Signs of the loosening of the epithelial union can be seen in the sixth month but it is ordinarily well into the seventh month before the eyelids actually reopen. The eyelashes are, of course, merely specialized hairs and their follicles develop by essentially the same series of stages illustrated in Fig 135. They have rather rudimentary sebaceous glands (glands of Zeis) associated with them and are peculiar in having also modified sweat glands (glands of Moll) opening into the lumen of the follicle. On the external surface of the eyelids the epithelium becomes the stratified squamous keratinized type, similar histologically to other areas where the skin is thin and devoid of any but fine rudimentary hairs. At the margin the epidermal type of epithelium is reflected for a short distance inside the lid as the so-called ad-marginal zone. Except for this narrow zone of transition, the epithelium on the inner face of the lid becomes stratified columnar. It is kept moist by the secretion of numerous small glands of the same type as the main lacrimal glands, and lubricated by the mucous secretion of unicellular glands of the goblet cell type. This epithelium together with its connective-tissue tunica propria constitutes the *conjunctiva*. The conjunctiva extends from the inner surface of the lids onto the sclera and at the sclerocorneal junction becomes continuous with the modified transparent epithelium of the cornea. The space between the eyelids and the front of the eyeball is commonly referred to as the *conjunctival sac*.

Along the margin of each lid is developed a row of about 30 *tarsal glands* (*glands of Meibom*). These glands are sebaceous in character though their form differs somewhat from that of the typical sebaceous glands opening into hair follicles.

The most massive glands opening into the conjunctival sac are the *lacrimal glands*. They develop from multiple buds which make their first appearance during the ninth week. These buds arise from the conjunctival epithelium of the lateral part of the upper lid, about where it turns back to be reflected over the sclera. The deep portions of the acini derived from these six to ten—or even twelve—buds tend to merge into a common glandular mass. Late in its development the gland as it expands is constricted by the tendinous extension of the levator palpebrae superioris muscle. This gives rise to the partially separated condition which has led to the designation in descriptive anatomy of a superior and inferior lacrimal gland. The lacrimal glands produce a thin watery secretion which under normal conditions keeps the corneal surface cleaned and lubricated. When stimulated by local irritation, or under conditions of emotional disturbance, activated by way of the autonomic nervous system they produce fluid in excess, which overflows the lids as “tears.”

The fluid produced by the lacrimal glands is drained from the conjunctival sac into the nasal chamber. An upper and a lower lacrimal duct, arising at the medial angle of the upper and lower lids respectively, join each other and are continued as the nasolacrimal duct which discharges into the nose under the inferior concha (Fig. 230, C). The manner in which the nasolacrimal duct is established by the closing over of the naso-optic furrow is dealt with further in connection with the development of the face. (See Chapter 14 and Figs. 247, 248.)

Changes in Position of the Eyes During development the eyes undergo a striking change in their relative position. In embryos of the sixth week they are far apart on either side of the head (Figs. 247, C, 248, C). If, at this stage, a line is imagined passing through the optical axis of each eye and then prolonged to meet in the center of the head, the angle these two lines would form would be about 160° . In other words, the eyes look almost straight off to either side like the eyes of a fish. In such a position there can be no overlapping of their visual fields which precludes the binocular type of vision so important to us in estimating distances. As the facial structures grow, the eyes are carried forward in the head and as a result their optical axes begin to converge. By the end of the seventh week (embryos of 17 to 19 mm) the ocular angle has been reduced to about 120° . By eight weeks the eyes are beginning to look quite definitely forward (Fig. 247, F) and by the tenth week (embryos of 40 to 50 mm) the angle is down around 70° —only about 10° wider than it is in the adult.

Congenital Defects of the Eye As one might suspect from the intricacy of the growth processes involved, the eye is vulnerable to a great number of different types of developmental defects, some very serious and others more in

the nature of slight variations from the standard pattern. As a companion volume to her book on "The Development of the Human Eye," Dr. Ida Mann has written a very comprehensive treatise on "Developmental Abnormalities of the Eye" which should be consulted by anyone interested in this special field. Here we may merely discuss briefly some of the more commonly encountered defects, and call attention to a few others that, although rather uncommon, are of special interest clinically, or from the standpoint of developmental mechanisms.

By all odds the commonest developmental defect of the eyes is faulty curvature of the cornea or the crystalline lens such that the image of a luminous point is not brought into sharp focus on the retina but appears spread out as a line. This condition, known as *astigmatism*, is one of the usual defects for which corrective eyeglasses are worn. Irregularities in the proportions of the eyeball may also interfere with the production of a sharp image. If the eyeball is too long in the direction of its optical axis, the rays are brought to focus in front of the retina and the individual is near-sighted (*myopic*). Conversely, if the eye is flattened so it is too short in the direction of its optical axis, the rays will come to focus beyond the retina, and the person is far-sighted (*hypermetropic*, or *hyperopic*).

The term *coloboma* is used in ophthalmology to designate an abnormal notch or gap in the eye. Such a notch may be limited to the iris, in which case it is designated as *coloboma iridis* (Fig. 238, A), or the gap may extend deeper and involve the ciliary body and even the retina. The more extensive *colobomata* occur almost invariably in the plane of the choroid fissure, and it seems probable that their incipience goes back to a failure of the choroid fissure to close. *Coloboma* limited to the iris usually is in the ventromedial segment of the optic cup where the choroid fissure closed, but there are a number of cases on record where the defect is definitely not in this location. It will be recalled that the choroid fissure closes toward the end of the sixth or beginning of the seventh week, and that the iris is formed subsequently by growth of the margins of the optic cup. If there is a gap in the line of the old choroid fissure, and this gap does not go deeper than the iris, it can only be assumed that the margin of the cup for some unknown reason failed to grow at the point where the choroid fissure fused. The fact that the gap may occur in other locations is further evidence that in cases where the *coloboma* involves the iris alone, we are dealing with a disturbance in the growth of the margins of the cup referable to a phase of development later than the time of closure of the choroid fissure.

There is occasionally a *failure of the pupillary membrane to resorb*. Rarely does the membrane persist intact. Usually resorption has progressed to a considerable extent, leaving perhaps a few small masses of connective tissue suspended over the pupil by delicate strands (Fig. 238, B, C). Persistence of vestiges of the hyaloid branches which fed the *tunica vasculosa lentis* during embryonic life is a comparable condition in that there is retention of a structure ordinarily resorbed in the course of development. In this case, also,

the persistence is usually only partial with varying degrees of resorption having been accomplished. In contrast with a persistent pupillary membrane which is in front of the lens, the hyaloid remnants offer an obstruction behind the lens, that is between it and the retina (Fig 238, E). Vestiges of the main hyaloid artery may persist near its point of entrance into the eyeball (Fig 238, D) but unless the persistent portion of the vessel is unusually long it causes little if any disturbance of vision.

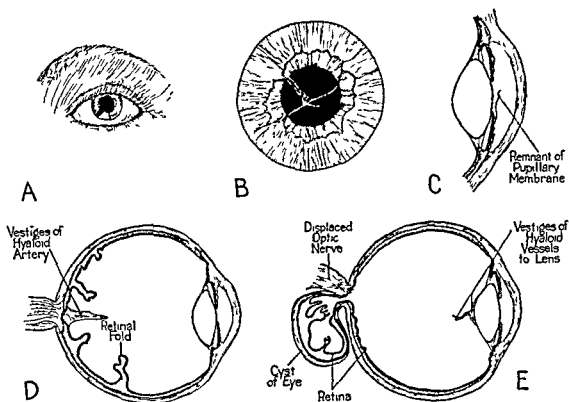


FIG 238 Diagrams showing some of the less uncommon developmental anomalies of the eye (Adapted from a number of sources, chiefly Ida Mann) A, Coloboma iridis B, Persistent remnants of pupillary membrane C, Sectional plan showing how remnants of pupillary membrane are attached to iris D, Vestiges of hyaloid artery, and, also, abnormal retinal folds E, Cyst of the eyeball which has everted at a point of weakness where choroid fissure closed about entrance of optic nerve. Same eye shows vestiges of branches of hyaloid vessels behind lens where they spread out to feed the tunica vasculosa lentis

The term "cataract" is applied to a condition in which the lens loses its transparency and becomes cloudy or opaque. It is most commonly a degenerative change occurring in old age. Occasionally, however, a child is born with lenses that have either failed to become clear or have become secondarily opaque during development. This condition is known as *congenital cataract*. Recently a number of observations have been published which indicate that German measles in a pregnant woman, although it may cause little apparent disturbance in the mother, may be the cause of congenital cataracts in the eyes of her infant. Apparently the incidence of cataract is strikingly higher when the disease occurs in the second and third months of pregnancy. This is not surprising since this is the period in which the formation of the lens is

progressing most rapidly in the fetus, and it would naturally be more vulnerable at that time to whatever damaging agent gets across the placental barrier from the circulation of the mother into the fetal circulation. This if confirmed may well prove a discovery of very far-reaching importance. It would be the first authenticated instance in which a specific local congenital defect in the fetus could be attributed to a known disturbance in the mother during pregnancy.

One of the striking, though rare, congenital defects of the eye is the malformation known as an *optic cyst*. In this condition there is a herniation of the eyeball with a portion of the retina protruding into a scleral sac (Fig 238, E). Such cysts are most likely to form at what seems to be a point of weakness where the choroid fissure closed about the entering hyaloid artery. They may become of considerable size, displacing the optic nerve and causing the eye to protrude far out of its normal position in the orbit. Probably akin to optic cysts is the condition in which the retina is overvoluminous and is folded within the eyeball but without herniation (Fig 238, D).

The outer layer of the retina may fail to accumulate the pigment granules that normally form there in abundance. Such a deficiency in pigmentation interferes with the mechanism shielding the photosensitive cells of the retina against strong light and the individual tends to be photophobic. In its extreme form a deficiency in pigmentation is usually part of the picture of a general albinism. The eyes of such individuals are readily recognizable because the lack of pigment in the iris leaves it a very pale watery blue.

When the circular venous sinus (canal of Schlemm) or the spaces (of Fontana) draining into it fail to form so that there is a lack of normal drainage of the contents of the eyeball, a condition known as *congenital glaucoma* results. The increase in intra-ocular pressure in glaucoma, if uncontrolled, may be sufficient to cause irreparable damage to the retina, ending ultimately in blindness.

Among the extreme distortions—which fortunately are very rare—are complete or nearly complete absence of the lens (*aphacia*), absence of the entire eye (*anophthalmia*) and fusion of the two eyes to form a single median eye (*cyclopia*). In cyclopic individuals the eye fusion may be complete, or varying degrees of duplicity may still be apparent. The distortion that results in cyclopia usually involves other structures in the front of the head. A common concomitant of cyclopia is a nose in the form of a cylindrical, proboscislike mass of flesh pendent from the nasal region or the forehead (Fig 255, E). In very rare instances the two nasal primordia fail to fuse with each other and each forms a cylindrical mass of flesh representing half of a nose. Such double proboscides may be related in very bizarre fashion to a cyclopic eye (Fig 255, F).

THE EAR

The adult mammalian ear may be divided for convenience in consideration into three regions: external, middle, and internal. The external ear is

essentially a sound-collecting funnel consisting of the auricula or pinna and the external auditory canal. The middle ear is a sound-transmitting mechanism involving the chain of three auditory ossicles which pick up the vibrations received by the eardrum and transmit them across the middle ear, or tympanic cavity, to the receptive mechanism of the internal ear. The internal ear is composed of an elaborate system of fluid-filled, epithelially lined chambers and canals constituting the so-called membranous labyrinth. This membranous labyrinth lies within the temporal bone in a similarly shaped, but larger, series of cavities constituting the bony labyrinth. The narrow space between the walls of the bony labyrinth and the membranous labyrinth is known as the perilymphatic space and is filled with the perilymphatic fluid. The sound-receiving portion of the membranous labyrinth is the cochlea, a curiously shaped mechanism spirally coiled in a manner suggestive of a snail shell. Closely associated with the cochlea is the so-called vestibular complex concerned with equilibration. The vestibular portion of the membranous labyrinth is composed of the sacculus, the utricle, and the three semi-circular ducts, or canals. It is phylogenetically the most primitive part of the ear—in fact, it is the only part of the ear that has been differentiated in the fishes.

Formation of Auditory Vesicle The primordium of the membranous labyrinth is the first part of the ear mechanism to make its appearance. In

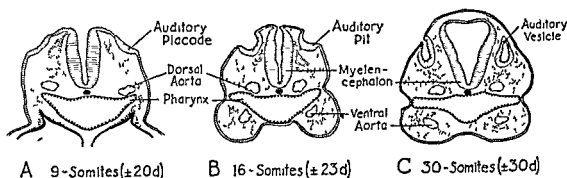


FIG. 239 Formation of auditory vesicle as seen in cross-sections of young human embryos (Modified from Arcy.)

embryos early in the third week (two-somite stage, Fig. 48) there is a vaguely marked thickening of the superficial ectoderm on either side of the still open neural plate. This thickening is the start of the *auditory placode* which, by the middle of the third week (seven-somite stage, Fig. 49), becomes quite clearly marked. By the end of the third week the auditory placode has taken shape as a sharply circumscribed thickening in the ectoderm on either side of the developing myelencephalon (Fig. 239, A). During the fourth week the placode is invaginated to form the *auditory pit* (Fig. 239, B). The pit becomes deepened and finally its opening at the surface is closed and the epithelium lining it comes to constitute a closed sac known as the *auditory vesicle* (*otic vesicle*).

Differentiation of Auditory Vesicle to Form Membranous Labyrinth
 As the auditory vesicle enlarges it changes from its originally spheroidal shape

and becomes elongated dorsoventrally. About where the epithelium of the auditory vesicle separated from the superficial ectoderm, there develops a tubular extension of the vesicle known as the endolymphatic duct (Fig 243, A). As the auditory vesicle expands laterally, the endolymphatic duct is left occupying a progressively more median position in relation to the rest of the vesicle. Almost from the outset of its differentiation the more expanded dorsal portion of the auditory vesicle with which the endolymphatic duct is connected can be identified as the primordium of the vestibular part of the membranous labyrinth, and the more slender ventral extension is recognizable as the primordium of the cochlea (Fig 240).

By the close of the sixth week of development conspicuous flanges appear on the vestibular portion of the auditory vesicle foreshadowing the differentiation of the *semicircular ducts*. As the flanges push out from the main vesicle their central portions become thin and finally undergo resorption so that the original semilunate flange becomes converted into a looplike duct (Fig 240, C-E). There are three such ducts (canals) formed, each occupying a plane in space approximately at right angles to the other two. In animals in the primary quadruped position these canals are designated as anterior vertical, posterior vertical, and horizontal. In man with his erect posture the anterior vertical canal is usually known as the superior, the posterior vertical as the posterior, and the horizontal as the lateral. Either terminology is so self-evident that the departure of the human nomenclature from that of comparative anatomy is less troublesome in this instance than in certain others. While the *semicircular ducts* have been taking shape the vestibular portion of the auditory vesicle becomes subdivided by a progressively deepening constriction into a more dorsal utricular portion and a more ventral saccular portion (Fig 240, E-G). When this division has occurred, the *semicircular ducts* open off the utricle. Near one of their two points of communication with the utricle, each *semicircular canal* forms a local enlargement known as an *ampulla*. Within the *ampulla* there develops a specialized area called a *crista*, containing neuro-epithelial cells with hairlike processes projecting into the lumen of the *ampulla*. These specialized receptors are innervated by branches of the vestibular division of the eighth cranial nerve. Changes in the position of the head are accompanied by a lag in the movement of fluid within the *semicircular ducts* which results in mechanical stimulation of the neuro-epithelial cells of the *crista*. The nerve impulses thus initiated pass over the appropriate central pathways (Fig 194) and make us aware of positional changes. In the light of this function the significance of the arrangement of the three *semicircular ducts* in planes at right angles to each other is self-evident.

Specialized areas, called *maculae*, are developed in the sacculus and utricle. The *maculae* contain neuro-epithelial cells similar in general character to those in the *cristae* of the *semicircular ducts*, and like them supplied by branches of the vestibular division of the eighth cranial nerve. It is in the *maculae* that the impulses are initiated which make us aware of static posi-

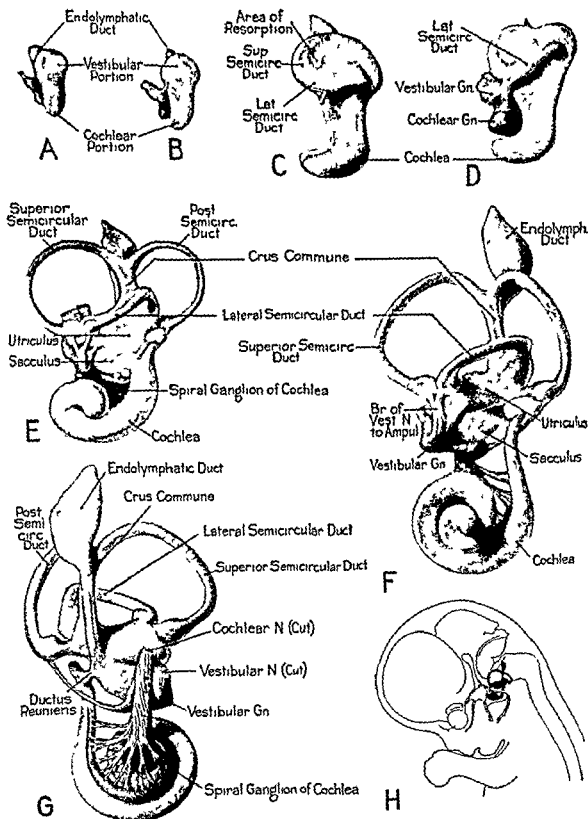


FIG 240 Development of the membranous labyrinth (After Streeter, *Am J Anat*, Vol 6, 1906) A, 6 mm, lateral view B, 9 mm, lateral view C, 11 mm, lateral view D, 13 mm, lateral view E, 20 mm, lateral view F, 30 mm, lateral view G, 30 mm, medial aspect H, Outline of head of 30 mm embryo to show position and relations of developing inner ear

tion in distinction to the sense of positional change as mediated through the mechanism of the semicircular canals

The *cochlear portion of the membranous labyrinth* elongates rapidly during the sixth week and in embryos of 11 to 13 mm it shows a sharp forward bend of its distal end (Fig 240, C, D) Elongation continues at an accelerated rate during the seventh and eighth weeks and the initial bend rapidly develops into a spiral of two and one-half turns (Fig 240, E-F) As the cochlea is thus differentiated its originally broad connection with the vestibular portion of the membranous labyrinth becomes narrowed to the slender ductus reuniens (Fig 240, G) The cochlear division of the eighth nerve follows the cochlea in its growth changes, and its fibers fan out to be distributed along the entire length of the cochlear duct Adjacent to the cochlear duct is formed a band-like ganglion, appropriately called, because of its configuration, the *spiral ganglion of the cochlea* The actual tone-receptive mechanism inside the cochlea with which the cells of the spiral ganglion make connection is the *organ of Corti* The development of the organ of Corti can be considered most conveniently a little later when the relations of the membranous labyrinth within the bony labyrinth have been outlined

Development of Bony Labyrinth and Perilymphatic Spaces By the early part of the third month of development the membranous labyrinth has attained practically its adult configuration (Fig 240, F, G) There remain only such minor changes as the separation of the sacculus and utriculus so they are in communication through a Y-shaped connection with the endolymphatic duct, and the elongation and attenuation of the ductus reuniens While the membranous labyrinth has been taking shape, there has been a gradual concentration of mesenchyme about it and by the time the epithelial part of the complex has assumed approximately its definitive form the surrounding mesenchyme has been transformed into cartilage (Fig 243) Between the membranous labyrinth and the cartilage in which it is embedded there remains some space partially occupied, at first, by loosely aggregated mesenchymal cells Toward the cartilage these cells become organized into a perichondrial connective-tissue layer About the primary epithelial sacs and ducts of the membranous labyrinth the adjacent mesenchyme becomes organized into a fibrous outer investment Between the walls of the membranous labyrinth, thus reinforced, and the surrounding cartilage, delicate strands of connective tissue are developed suspending the membranous labyrinth within the cartilaginous labyrinth (Fig 241, B) The very loose meshes of this supporting tissue traverse a space known as the perilymphatic (periotic) space which is filled with a fluid similar to cerebrospinal fluid in its composition

The arrangement of the perilymphatic spaces about the cochlea is of special interest because of its importance in sound conduction By looking ahead at a diagram showing the way the ossicles transmit vibrations from the eardrum across the middle ear it will be apparent that the movements of the footplate of the stapes activate a membrane in the oval window (Fig 244) Vibrations are thus imparted to the perilymph about the base of the cochlea

Because of the way the cochlear duct is stretched across the center of the spiral bony canal in which it lies, these fluid vibrations can pass along the perilymph space above the cochlear duct (*the scala vestibuli*), go through an open area at the apex of the cochlear spiral (*helicotrema*), and pass along the perilymph space below the cochlear duct (*scala tympani*) (Fig 241, A) A small membrane in the round window provides compensating resilience so that the fluid waves starting at the oval window are not dampened out as they would be if the fluid were confined in completely rigid walls The organ of hearing, being suspended in the fluid-filled cochlear duct between the scala

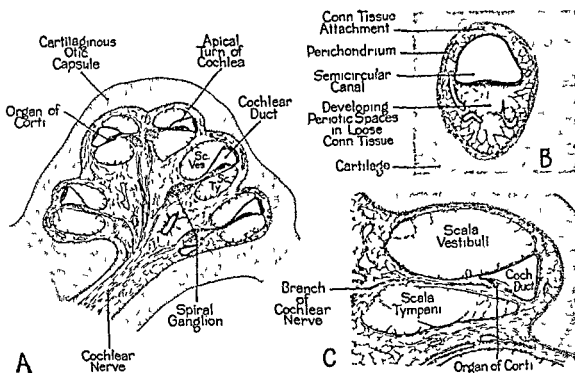


FIG 241 The relations of the supporting tissues and perilymphatic spaces to the developing membranous labyrinth in fetuses of the fourth month A, Semi-schematic plan of cochlea (Adapted from several sources) B, Section through semicircular canal (After Streeter, Carnegie Cont to Emb, Vol 7, 1918) C, Section through a turn of the cochlea showing the topography of the cochlear duct and the related periotic spaces (After Streeter, *ibid*)

vestibuli and the scala tympani (Fig 241, C), is in a position to pick up any vibrations imparted by the ossicles to this fluid system

The establishing of the relations outlined above takes place while the surrounding tissue is at first mesenchymal and then cartilaginous In both these phases it is plastic and readily remolded in conformity with the elaborate changes in configuration undergone by the developing membranous labyrinth With the basic relations of both parts established, the attainment of adult relations involves little more than the conversion of the cartilaginous ear capsule into bone by the spreading of multiple centers of endochondral ossification

Organ of Corti The actual tono-receptive mechanism of the ear is a ridge of modified epithelial cells in the cochlear duct These cells rest on the basilar

membrane which supports the cochlear duct in the bony canal. This cellular ridge, because of its characteristic shape, is called the spiral organ. It is also known, especially in the older literature, as the organ of Corti after the Italian anatomist who first accurately described it.

The first indication of the differentiation of the organ of Corti becomes apparent in embryos of the third month as a local thickening of the epithelium of the floor of the cochlear duct. Over this epithelial thickening there is formed a curious fibrillar and gelatinous structure known as the tectorial membrane (Fig 242, A). From the third to the fifth month the entire cochlear

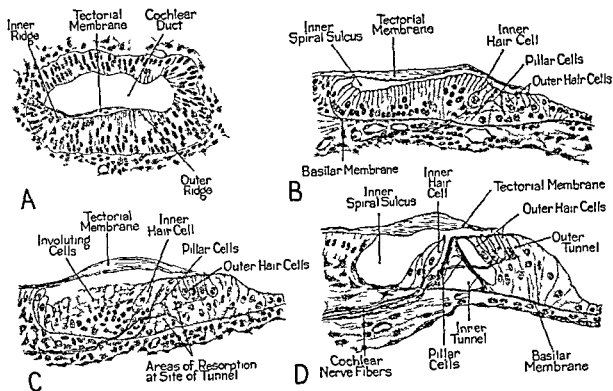


FIG 242 Four stages in the development of the organ of Corti (Redrawn, with some modifications, from Kolmer, in Mollendorf "Handbuch der Mikroskopischen Anatomie des Menschen," 1927) A, From an embryo of the eleventh week B, From an embryo of about five months C, From an embryo of about the same apparent age as that of B but developmentally more advanced D, Slightly schematized representation of the conditions at term

duct undergoes considerable expansion. The tectorial membrane becomes more extensive and the developing organ of Corti beneath it begins to show marked specialization. In its outer portion there are differentiated three to four rows of neuro-epithelial cells known as the *outer hair cells*. A little nearer the center of the spiral appears a single row of larger neuro-epithelial elements known as the *inner hair cells* (Fig 242, B). During the sixth month there is involution of some of the cells adjacent to the line of attachment of the tectorial membrane. This, together with some cell rearrangement, deepens the groove on the inner border of the organ of Corti to form the so-called *inner spiral sulcus* (Cf Fig 242, B, C). At the same time, there is some resorption within the organ of Corti itself, leaving a space between the inner and the outer hair cells called the *inner tunnel*, and a smaller space peripheral to

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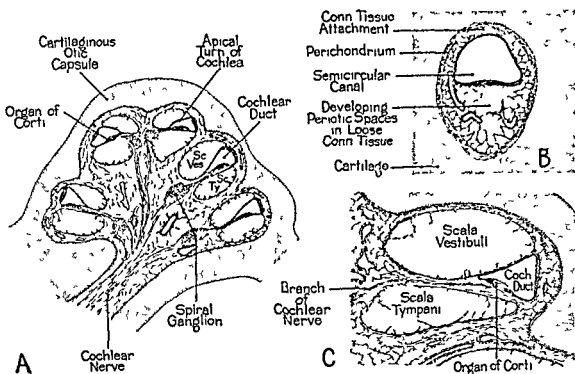


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Organ of Corti The actual tone-receptive mechanism of the ear is a ridge of modified epithelial cells in the cochlear duct These cells rest on the basilar

pulses are initiated in the terminal processes of the cochlear nerve fibers which form basketlike investments about the bases of the hair cells

Middle Ear At the same time that the receiving mechanism of the ear is being developed in the manner just described, the transmitting apparatus of the middle ear is also taking shape. It will be recalled that in their initial relations the first pharyngeal pouches extend laterad so that their entodermal lining makes contact with the ectoderm at the bottom of the first gill furrow on either side to form the gill plate (Fig 239, C). The distal portion of the pouch remains somewhat expanded to form the primordium of the middle-

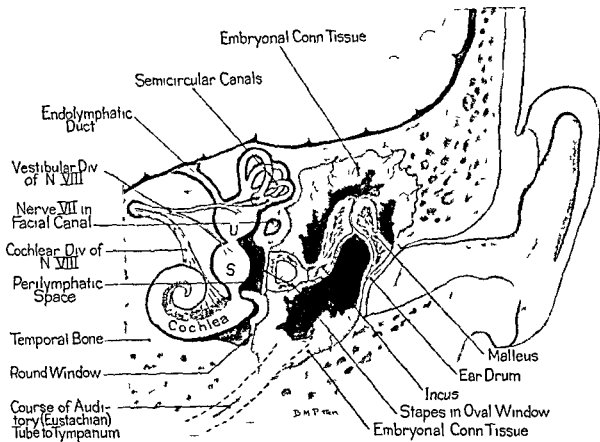


FIG 244 Schematic diagram showing structure of ear at term. For the sake of clarity the ossicles have been represented larger than their true size. The cochlea has been pulled out toward mesial side in order to show its spiral course.

ear chamber, or tympanic cavity, but the proximal portion soon becomes narrowed to form the auditory (Eustachian) tube (Fig 243, A, B). The primary contact between pharyngeal-pouch entoderm and the ectoderm of the floor of the gill furrow does not long persist. The blind outer end of the pouch, which constitutes the primordium of the tympanic cavity, pulls away from the surface and there appears adjacent to it a conspicuous concentration of mesenchyme (Fig 243, A). As development progresses the mesenchymal cells of this primordial mass become organized into the cartilage precursors of the auditory ossicles lying between the developing inner ear and the retained portion of the first gill furrow which may now be said to constitute the primordium of the external auditory meatus. At this stage the ossicles lie above the primordial tympanic cavity, completely embedded in a very loose embry-

the outer hair cells, known as the outer tunnel. Cells adjacent to the inner tunnel develop fibrils and become converted into supporting elements designated as the *pillar cells* (Fig. 242, D).

The physiology of this elaborate mechanism—especially the question of the discrimination of pitch—still involves matters subject to some controversy. The general nature of the processes, however, seems quite clear. The tectorial

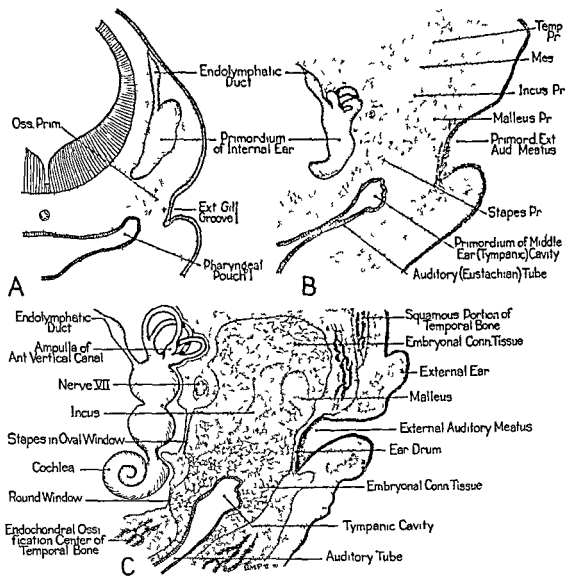


FIG. 243 Schematic diagrams showing three stages in development of auditory ossicles

membrane is adherent to the bristlelike processes at the distal ends of the neuro-epithelial cells. When movement of the eardrum is transmitted by the ossicles to the membrane across the oval window, a wave motion is set up in the perilymph fluid in which the cochlear duct lies suspended on the fibrous basilar membrane. The motion of the perilymphatic fluid causes changes in the relative positions of the basilar and tectorial membranes with resultant stimulation of the hair cells. From these neuro-epithelial elements nerve im-

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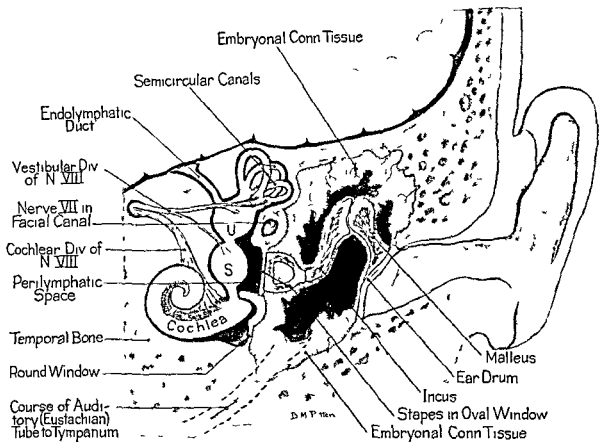


FIG 244 Schematic diagram showing structure of ear at term. For the sake of clarity the ossicles have been represented larger than their true size. The cochlea has been pulled out toward mesial side in order to show its spiral course.

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onal connective tissue During the latter part of *intra-uterine* life the connective tissue about the ossicles begins to undergo rapid resorption with a resultant expansion of the tympanic cavity Ultimately the ossicles come to lie suspended within the enlarged tympanic cavity with only a thin layer of epithelium reflected over their periosteal investment At the time of birth, however, there is still a residue of unresorbed embryonal connective tissue partially filling the tympanic space and more or less damping the free movement of the ossicles (Fig 244)

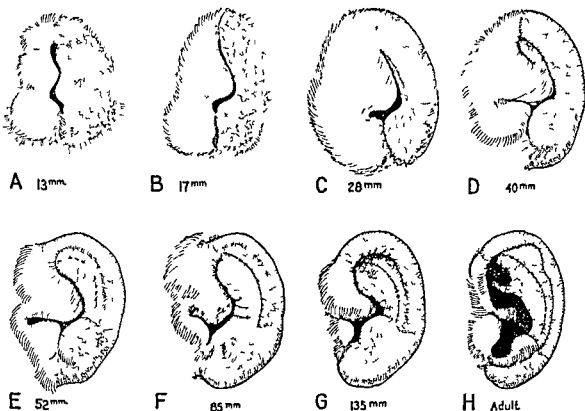


FIG 245 Stages in development of external ear (After Streeter, *Carnegie Cont to Emb*, Vol 14, 1922) The parts derived from the mandibular side of the cleft are unshaded, the parts from the hyoid side are indicated by stippling and by irregularly placed dashes

The full movability of the ossicles is acquired within a few months after birth when the remaining loose connective tissue is absorbed When this has occurred movement imparted by sound waves to the eardrum is freely transmitted by the ossicles to the membrane of the oval window to which the stapes is attached

The point at which the ossicles are suspended by their ligaments is such that the activating side of the lever system which they constitute is the longer part, thus tending to increase the power delivered by the impact of the stapes at the oval window The mechanical advantage in transmission is further increased by the fact that the area of the eardrum is some 20 times as great as that of the oval window Actually, of course, there is considerable energy lost in transmission due to the inertia of the ossicles and the damping effect of

the air in the tympanic cavity, but the net power gain in the system remains considerable

External Ear The pinna of the ear is formed by the growth of the mesenchymal tissue flanking the first (hyomandibular) gill furrow of the young embryo. During the second month a group of nodular enlargements appear, some of them arising from mandibular arch tissue rostral to the first gill furrow, and others from the hyoid arch along the caudal border of the furrow. The coalescence of these tubercles and their further development molds the pinna of the ear (Fig 245). In view of the number of separate growth centers involved it is not surprising that the configuration of the fully formed external ear exhibits a wide range of variations. These individual differences are easy

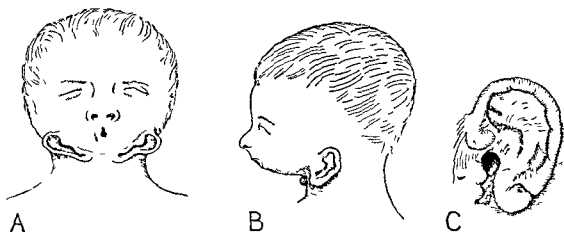


FIG 246 Abnormalities of the external ear. A, Micrognathia with external ears remaining in the primitive hyomandibular cleft position (Sketched from specimen 3083 in the Konigl Path Mus., Berlin.) B, Similar case in lateral view from the Heidelberg Museum (From Streeter, after Schwalbe.) C, Incomplete fusion of the tubercles about the hyomandibular cleft (cf Fig 245) with resultant formation of an abnormal auricle (Redrawn, slightly modified, after Arey.)

to overlook until one begins to give particular attention to the details of ear shapes. A little critical observation, however, will soon make it apparent why European police utilize the configuration of the ear as one of the very important features in the identification of persons in whom they are interested.

Anomalies of the Ear The most serious anomalies of the ear involve the internal part of the mechanism and give no external manifestation of their existence. Congenital deafness, for example, may be due to defective nerve connections, to imperfect development of the neuro-epithelial receptors, or to faulty formation of the auditory ossicles. In early postnatal life incompletely resorbed embryonal connective tissue about the ossicles may be involved in middle-ear infection, with the resulting formation of scar tissue and a consequent dampening of the free movement of the ossicles.

Defects of the external ear may be quite conspicuous without in any way interfering with hearing. Failure of the tubercles about the hyomandibular cleft to fuse with each other, or failure of some of these tubercles to grow normally, may produce a variety of malformations (Fig 246, C). Much more striking, and fortunately exceedingly rare, is the development of the external

onal connective tissue During the latter part of intra-uterine life the connective tissue about the ossicles begins to undergo rapid resorption with a resultant expansion of the tympanic cavity Ultimately the ossicles come to lie suspended within the enlarged tympanic cavity with only a thin layer of epithelium reflected over their periosteal investment At the time of birth, however, there is still a residue of unresorbed embryonal connective tissue partially filling the tympanic space and more or less damping the free movement of the ossicles (Fig 244)

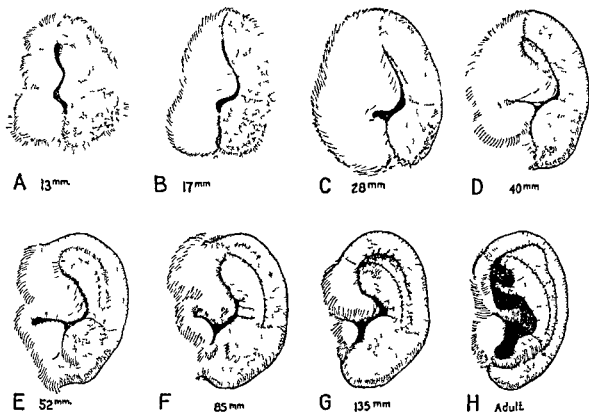


FIG 245 Stages in development of external ear (After Streeter, Carnegie Cont to Emb, Vol 14, 1922) The parts derived from the mandibular side of the cleft are unshaded, the parts from the hyoid side are indicated by stippling and by irregularly placed dashes

The full movability of the ossicles is acquired within a few months after birth when the remaining loose connective tissue is absorbed When this has occurred movement imparted by sound waves to the eardrum is freely transmitted by the ossicles to the membrane of the oval window to which the stapes is attached

The point at which the ossicles are suspended by their ligaments is such that the activating side of the lever system which they constitute is the longer part, thus tending to increase the power delivered by the impact of the stapes at the oval window The mechanical advantage in transmission is further increased by the fact that the area of the eardrum is some 20 times as great as that of the oval window Actually, of course, there is considerable energy lost in transmission due to the inertia of the ossicles and the damping effect of

14

Development of the Face and Jaws and the Teeth

FACE, JAWS, PALATE, AND TONGUE

In dealing with young embryos, many of the structures and growth processes involved in the early development of the cephalic region have been touched upon in one way or another. The precocious establishing of the neurocranial portion of the head is familiar. So, also, is the series of conspicuous gill arches which develop a little later and form the foundations of the visceral part of the head. In studying the early development of the digestive tract we saw that the primitive gut first appeared as a cavity which had neither oral nor anal opening but ended blindly at both its anterior and posterior ends (Fig. 70, A, B). We followed, also, the way in which an opening in the future oral region is established by the meeting of an ectodermal depression, the stomodaeum, with the cephalically growing anterior end of the gut (Fig. 70, D). The stomodaeal depression, even as late as the time the oral plate ruptures and establishes communication between the anterior end of the gut and the outside world, is very shallow (Fig. 56). The deep oral cavity characteristic of the adult is formed by the forward growth of structures about the margins of the stomodaeum. Some idea of the extent of this forward growth can be gained from the fact that the tonsillar region of the adult is at about the level occupied by the stomodaeal plate before it ruptured and disappeared. The growth of the structures bordering the stomodaeum then, not only gives rise to superficial parts of the face and jaws, but actually builds out the walls of the oral cavity itself.

The Jaws Because the front of the head of a young embryo is pressed against its thorax, it is not possible in the usual lateral views (Figs. 58-60) to see much of the interesting developmental changes going on in the facial region. It is necessary to study, in addition, specially prepared mounts of the head which can be so oriented as to provide direct views of the face. In such a preparation of a four-week embryo (Figs. 57, 247, A) the most conspicuous landmarks are the stomodaeal depression, and the mandibular arch which constitutes its caudal boundary. Within the next week most of the structures which take part in the formation of the face and jaws are already clearly distinguishable (Fig. 247, B). In the mid-line, cephalic to the oral cavity, is a rounded overhanging prominence known as the frontal process

ears on the upper part of the neck, with their lobes pointing toward the midline and not far apart. This is a retention of the primitive hyomandibular cleft position (cf. Figs. 246, A and 247, D) and is almost invariably associated with failure of the mandible to get its normal growth. When this failure of the mandible to develop is extreme it is known as *agnathia*, when it is somewhat less marked the condition is spoken of as *micrognathia*. It would seem probable that the lack of development of the mandible is the primary one of these associated defects, and that the primitive position of the ears persists because they are not forced around to the side of the head as is the case when the development of the lower jaw is normal.

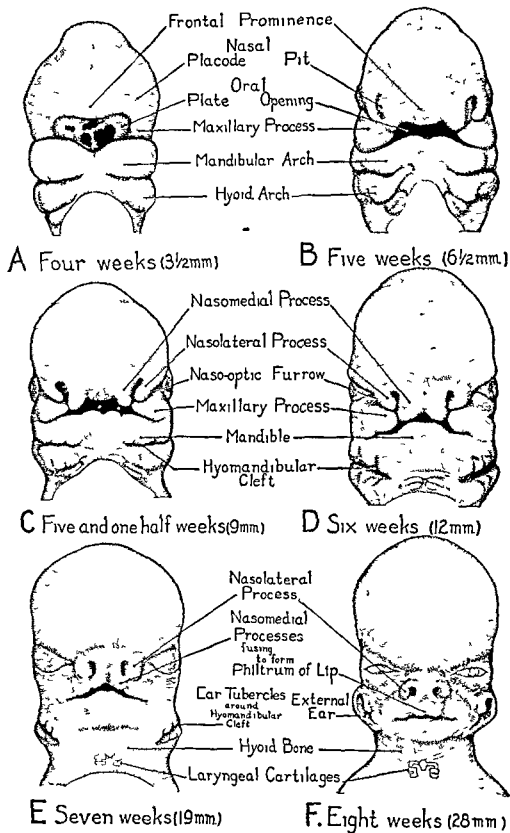


FIG 247 Drawings showing, in frontal aspect, some of the important steps in the formation of the face (After William Patten, from Morris "Human Anatomy")

On either side of the frontal process are horseshoe-shaped elevations surrounding the olfactory pits. The median limbs of these elevations are known as the nasomedial processes and the lateral limbs are called the nasolateral processes.

Growing toward the mid-line from the cephalolateral angles of the oral cavity are the maxillary processes. In lateral views of the head (Figs 58-60) it will be seen that the maxillary process and the mandibular arch merge with each other at the angles of the mouth. Thus the structures which border the oral cavity cephalically are (1) the unpaired frontal process in the mid-line, (2) the paired nasal processes on either side of the frontal process, and (3) the paired maxillary processes at the extreme lateral angles (Fig 247, B). From these primitive tissue masses are derived the upper lip, the upper jaw, and the nose.

The caudal boundary of the oral cavity is less complex, being constituted by the mandibular arch alone. In very young embryos (Fig 247, A) the origin of the mandibular arch from paired primordia is still clearly evident. Appearing first on either side of the mid-line are marked local thickenings due to the rapid proliferation of mesenchymal tissue. Until these thickenings have extended from either side to meet in the mid-line there remains a conspicuous mesial notch, with their fusion, the arch of the lower jaw is completed (Fig 247, B-F).

During the sixth week (Fig 247, C-D), very marked progress is made in the development of the upper jaw. The maxillary processes become more prominent and grow toward the mid-line, crowding the nasal processes closer to each other. The nasal processes, meanwhile, have grown so extensively that the lower part of the frontal process between them is completely overshadowed (Cf Figs 247, B, D). The growth of the medial limbs of the nasal processes has been especially marked and they appear almost in contact with the maxillary processes on either side. The groundwork for the formation of the upper jaw is now well laid down. Its arch is completed by the fusion of the two nasomedial processes with each other in the mid-line, and with the maxillary processes laterally (Fig 247, E, F).

Toward the close of the second month, when the molding of the soft parts is well under way, formation of the deeper-lying bony structures begins. The more medial portion of the maxillary bone which carries the incisor teeth arises from separate ossification centers formed in the part of the upper jaw which is of nasomedial origin. This independent origin of the incisive portion of the human maxilla emphasizes its homology with what in lower forms a separate bone known as the premaxillary or intermaxillary. In the skulls of human infants the sutures separating the incisive portion from the rest of the maxilla are still evident, and occasionally traces of them may be made out in the adult skull. The rest of the maxillary bone, carrying all the upper teeth behind the incisors, is developed in the part of the upper jaw which arises from the maxillary process. It is one of the first bones in the body to be calcified (Figs 172-174).

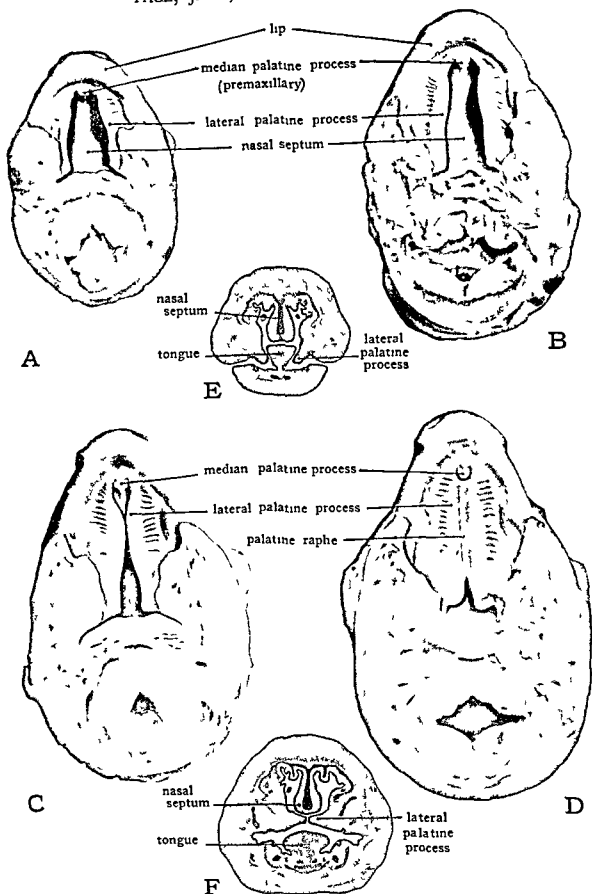


FIG 250 Photographs ($\times 5$) of dissections of pig embryos made to expose roof of mouth and show development of palate A, 20.5 mm, B, 25 mm, C, 26.5 mm, D, 29.5 mm. The diagrams of transverse sections are set in to show the relations before (E) and after (F) the retraction of the tongue from between the palatine processes.

These paired structures partition off the more cephalic portion of the original stomodaeal chamber. Since it is into this cephalic portion of the old stomodaeal cavity that the nasal pits break through, the formation of the palate in effect prolongs the nasal chambers backward so they open eventually into the region where the oral cavity becomes continuous with the pharynx.

The palate as well as the arch of the upper jaw is contributed to by both the nasomedial processes and the maxillary processes. From the premaxillary (naso-medial) region a small, triangular, median portion of the palate is

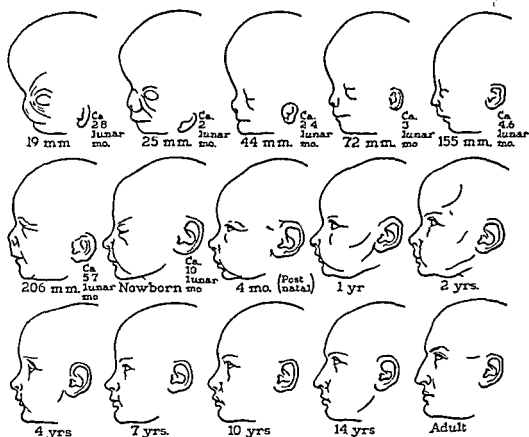


FIG. 249 Series of 15 left lateral views of head and facial region in embryo, fetus, newborn, infant, child, and adult (From Scammon, in Morris "Human Anatomy," after figures of Vogt, Keibel and Elze, Retzius, and Schadow)

formed (Fig. 250, A, B). The main part of the palate is derived from that portion of the upper jaw which arises from the maxillary processes. Shelf-like outgrowths arise on either side and grow toward the mid-line (Fig. 250, A, B). When these palatal shelves first start to develop the tongue lies between them and they are directed obliquely downward so their margins lie along the floor of the mouth on either side of the root of the tongue (Fig. 250, E). As development progresses, the tongue drops down and the margins of the palatal shelves swing upward and toward the mid-line (Fig. 250, F). Further growth brings them into contact with each other and their fusion soon completes the main part of the palate (Fig. 250, D). In the extreme rostral region the small triangular premaxillary (median palatine) process lies between the lateral palatine shelves and they fuse with it instead of with

Well-defined primordial masses of pre-muscle tissue can be identified in the floor of the pharynx directly opposite the origin of the twelfth (hypoglossal) nerve. This mass of developing muscle merges without any perceptible line of demarcation into the mesenchyme which underlies the floor of the oro-pharynx farther rostrad. Its exact extent can not be determined either by dissection or by the study of serial sections. It should, therefore, be emphasized that illustrations such as Figs. 189 and 190, which show a circumscribed mass of tongue muscle, have been highly schematized in the light of information derived from lower forms. Although it is difficult, in human embryos, accurately to trace the forward migration of the tongue muscles themselves, the changing relation of the twelfth nerve which is associated with them makes the main outline of the story sufficiently evident. As the muscle mass pushes forward underneath the mucosal layer of the tongue, the nerve follows along with it, so the course of the nerve in older embryos (Fig. 217) and in the adult (Fig. 218) clearly suggests the general path followed by the lingual muscles in their forward migration during development. The fact that in operative work a median incision of the tongue can be made with very little bleeding indicates the way the muscle masses and their associated blood vessels have remained clear of the mid-line, on either side of which they arose as paired primordia.

Developmental Defects of the Face, Jaws, and Palate Because they are not concealed within the body, or by clothing, developmental defects in the region of the face and jaws are quite generally familiar. The regions most frequently involved are the upper lip, jaw, and palate. The common designation of a cleft upper lip as a "harelip" is usually a misnomer, for the characteristic cleft in the lip of a hare, or a rabbit, is in the mid-line and, except in exceedingly rare instances, an abnormal cleft in the human lip appears to one side or the other of the mid-line (Fig. 253, A). It is quite obvious that such a defect is located at the line where, during the second month of development, the maxillary process should have fused with the nasomedial process (Fig. 247). As to the possible causes underlying such a failure of fusion, our knowledge is less satisfactory. Such defects have been attributed rather generally to some disturbance in intra-uterine living conditions which was supposed to be operative at the time the growth processes leading toward the fusion were in a critical phase. Of late an increasing amount of evidence points toward a more remote cause involving a gene defect. The accumulating data—still admittedly inadequate—seem to indicate that the condition is inherited, behaving as a Mendelian recessive.

A cleft lip may be unilateral or bilateral, and may or may not be accompanied by a cleft palate. Generally when the defect in the lip is extensive, both the jaw and the palate are likely to have been affected by the same developmental disturbance (Fig. 253). The defect in the jaw and in the anterior part of the palate is along the same line of fusion between nasomedial and maxillary processes which is involved in a cleft lip. Farther back in the palate the gap is medial, being due to the failure of the lateral palatal shelves to unite with each

ventral areas of the second and third, and, to a lesser extent, the fourth visceral arches. The fact that the ninth (glossopharyngeal) nerve is the chief sensory nerve to the base of the tongue is exactly what one would expect from the position of origin of this part of the tongue covering, and the primary relations of the ninth nerve to the visceral arches involved (Figs 216-218). Equally natural is the innervation of a small area at the extreme posterior

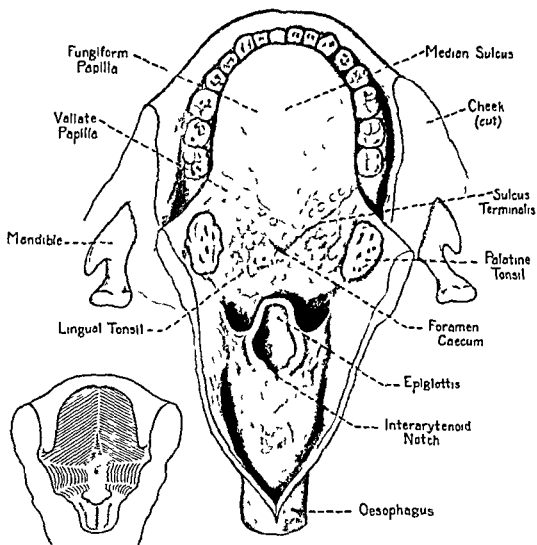


FIG 252 Tongue, floor of mouth, and pharyngeal region of the adult (In part after Corning) Pharynx has been cut open from behind to expose epiglottis and entrance to larynx. The small sketch, lower left, suggests the parts of the tongue of different embryological origin—for explanation of Fig 251

part of the tongue by the tenth (vagus) nerve, for it is this small region near the epiglottis that arises from fourth arch tissue.

Phylogenetically, the lingual muscles are known to be derived from bilaterally located mesodermal masses arising at segmental levels caudal to the point of origin of the tongue covering. The ontogenetic recapitulation of this process in human embryos is, however, so slurred over that it is difficult to trace except in suggestive outline. No direct evidence of the suspected ultimate origin from the occipital myotomes is available, but in five-week embryos

ill-defined primordial masses of pre-muscle tissue can be identified in the floor of the pharynx directly opposite the origin of the twelfth (hypoglossal) nerve. This mass of developing muscle merges without any perceptible line of demarcation into the mesenchyme which underlies the floor of the oro-pharynx farther rostrad. Its exact extent can not be determined either by dissection or by the study of serial sections. It should, therefore, be emphasized that illustrations such as Figs 189 and 190, which show a circumscribed mass of tongue muscle, have been highly schematized in the light of information derived from lower forms. Although it is difficult, in human embryos, accurately to trace the forward migration of the tongue muscles themselves, the changing relation of the twelfth nerve which is associated with them makes the main outline of the story sufficiently evident. As the muscle mass pushes forward underneath the mucosal layer of the tongue, the nerve follows along with it, so the course of the nerve in older embryos (Fig 217) and in the adult (Fig 218) clearly suggests the general path followed by the lingual muscles in their forward migration during development. The fact that in operative work a median incision of the tongue can be made with very little bleeding indicates the way the muscle masses and their associated blood vessels have remained clear of the mid-line, on either side of which they arose as paired primordia.

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other (cf Figs 250, 253) Such defects leave the oral and nasal chambers in open communication and cause an unmistakable thickness of speech in addition to the facial disfigurement Fortunately, modern surgery can do much toward repairing such conditions provided the infant is immediately placed in the proper hands It can not be too strongly emphasized that, the longer such a condition is allowed to go without the instituting of proper corrective measures, the less likely are satisfactory end-results

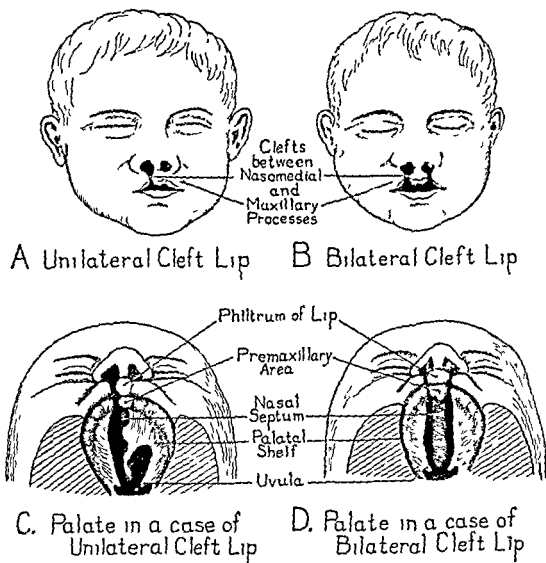


FIG 253 Cases of cleft lip and cleft palate (Modified from Corning)

Many defects less common than simple cleft lip and palate will be seen in any large oral surgery clinic Occasionally in cases of bilateral cleft lip and palate the premaxillary portion of the upper jaw, being entirely unattached to the maxillary processes, is carried forward by the growth of the nose so that it is completely out of line with the rest of the jaw (Fig 254, D) Although exceedingly rare, median clefts of the upper jaw sometimes occur (Fig 254, A) where the nasomedial processes of either side ordinarily fuse with each other during the seventh week (Fig 247, D, E) Thus uncommon defect

properly could be called a "harelip." Still more uncommon is a median cleft in the lower jaw which may occur as a result of the failure of the right and left components of the mandibular arch to unite with each other (cf Figs 247, A,

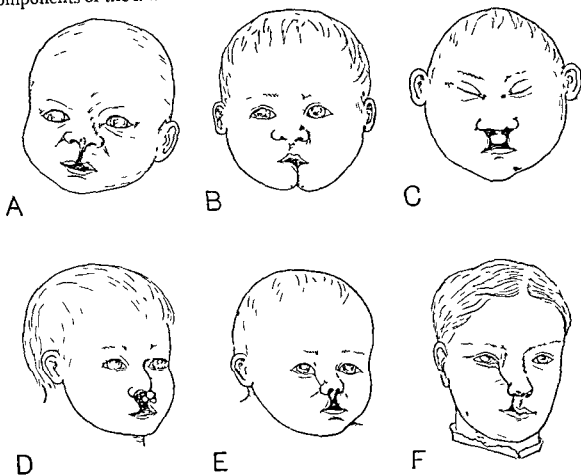


FIG 254 Developmental defects of the face occurring along lines where fusion of growing parts should normally occur

A, Median cleft of upper lip (From Schwalbe) This is a very uncommon type of defect in which the two nasomedial processes have failed to fuse with each other

B, Median cleft of the lower jaw (After Schwalbe) This also is a very uncommon defect due to failure of the two lateral halves of the mandibular arch to make union medially

C, Double cleft lips The lip defects are similar to those illustrated in Fig 253, B, but this infant is also microcephalic (Sketched from a specimen in the Dupuytren Museum, Paris)

D, Case of bilateral cleft lip in which the nasomedial components have been carried forward on the tip of the nose (Sketched from a case coming to autopsy in the Allgemeines Krankenhaus, Vienna)

E, Oblique facial cleft (unclosed naso optic furrow) combined with complete absence of the medial portion of the upper lip and jaw (Sketched from a specimen in the Path Anat Inst, Munich)

F, Oblique facial cleft combined with unilateral cleft lip (Modified from Schwalbe)

B and 254, B) Another defect which may occur is known as an oblique facial cleft or open nasolacrimal furrow (Fig 254, F) This condition is the result of the failure of the naso-optic furrow to close over as it does normally in the formation of the nasolacrimal duct. It usually occurs in combination with a cleft lip

In addition to defects of the foregoing types which clearly occur where embryological fusions have failed to take place, there are a variety of abnormalities due to local distortions of growth. A particular area, as for example the lower jaw, may lag in development. It may be just a little small for the rest of the face in which case we think of it as an individual peculiarity. In

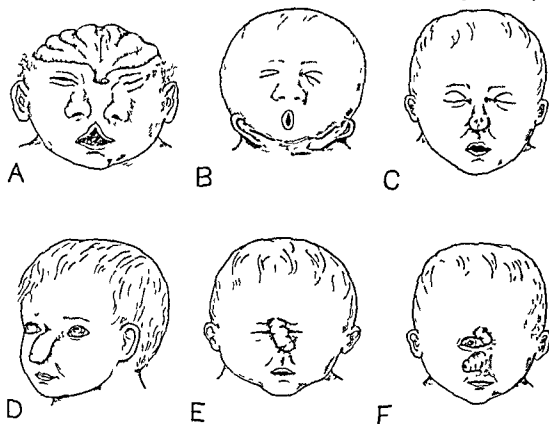


FIG. 255. Some of the rarer types of facial anomalies in which the underlying developmental defects are more complex than the fusion failures such as those illustrated in Fig. 254. (All, except B, sketched from specimens in the Path. Anat. Museum, Vienna.)

A, Divided nose and malformed mouth, also a defect in cranium so the meningeal covering of the brain is exposed.

B, Very poorly developed lower jaw (micrognathia) with external auditory meatus remaining nearly in the primitive gill-arch position. (Sketched from a specimen in the Konig Path. Museum, Berlin.)

C, Malformed, buttonlike nose with no nasal openings.

D, Malformed tubular nose without nasal openings.

E, Tubular nose overhanging a rudimentary and deeply embedded median eye.

F, Individual with well developed median eye (cyclops) and a tube-like protuberance above the eye in addition to one in the nasal region.

occasional cases the defect is so extreme that it distorts the entire proportions of the face and we then regard it as an anomaly called micrognathia. In such cases the position of the external ears is also involved. Not being crowded upward and backward by the normal growth of the jaws, they remain on the side of the neck in the primitive location of the hyomandibular cleft (Fig. 255, B). In the same general category of local growth deficiencies would come the cases in which the nose fails to form. There may, for example, be a buttonlike

nose with no nostrils, indicating a failure of the nasal pits to deepen and break through into the oral cavity (Fig 255, C)

Some of the conditions arising from local growth defects are of interest from other than the biological or medical standpoint. It is possible that they may have furnished the initial stimulus to the imagination which created some of the monsters of mythology. The Cyclops, one-eyed giants of Homer's *Odyssey*, may have come into being because some impressionable Greek saw an infant with but a single eye in the middle of its forehead (Fig 255, F). This malformation, known as cyclopia, is apparently due to a disturbance of the growth of the medial part of the forebrain at a very early stage of development which causes the primordial optic vesicles to converge toward each other and fuse to form a single median eye.

Not infrequently the disturbance which is responsible for a malformation is in the nature of exuberant or erratic growth rather than a local growth deficiency. Confronted by such a case we are likely to say that there has been a failure in the mechanism which normally regulates and directs growth. Although true enough, this is merely an erudite way of avoiding the admission that we do not know the real underlying causes. Examples in point are the curious proboscislike masses of tissue which sometimes occur at (Fig 255, D) or near (Fig 255, E, F) the location where the nose should have been found. There seems little doubt that such structures represent nasal processes which lack a nasal pit and have grown into bizarre forms. Although we are completely ignorant of the causal factors involved, such cases are, nevertheless, theoretically significant because they emphasize the fact that by no means all embryological defects are of the "developmental arrest" type.

THE TEETH

In primitive vertebrates the teeth are smaller, more numerous, and distributed over much wider areas than is the case in mammals. In their simplest form they are plates with conical protruding tips consisting of a core of calcified material called dentine, and an apical cap of much harder calcareous material called enamel. They are true dermal organs, for their dentine is formed by the connective-tissue layer of the skin, and their enamel by the epithelial layer. In the development of our own more highly specialized teeth it is interesting to see retained the same dual origin from epithelium and underlying mesenchyme. Even though our teeth start to form completely inside the gums instead of on a dermal surface, their enamel comes from specialized areas of epithelium which have grown down into the locations where the teeth are formed. Likewise their dentine comes from specialized mesenchymal cells of the same stock as the cells which give rise to the connective-tissue layers of the skin. When it is recalled that the epithelium which lines the tooth-forming part of the oral cavity is infolded stomodaeal ectoderm, we can see that, highly specialized as they are as to both structure and development, our own teeth have retained fundamentally the same origin in ontogeny as they had in phylogeny.

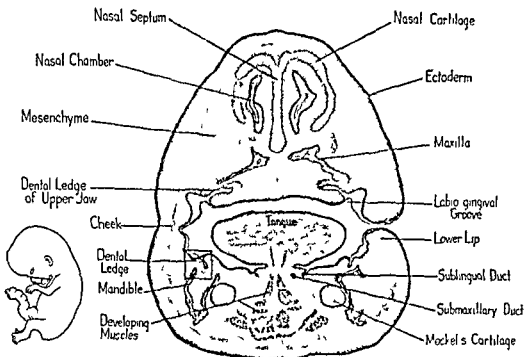


FIG 256 Projection drawing, $\times 20$, of a section through the jaws of a human embryo of the eighth week (University of Michigan Coll, EH 164, C-R, 25 mm) Outline, lower left, shows actual size of embryo, and the line across the jaws gives the location of the section The rectangle about the dental ledge indicates the area represented at higher magnification in Fig 257

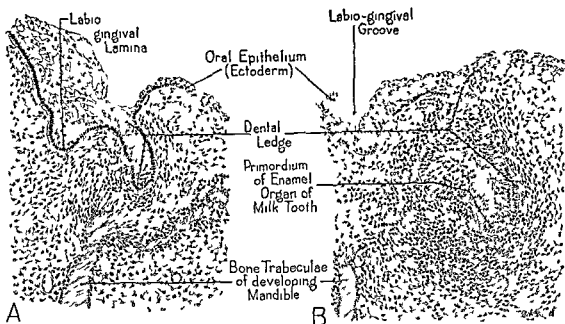


FIG 257 A, Projection drawing ($\times 150$) of the dental ledge of a human embryo of the eighth week The drawing was made from the area indicated by the rectangle in Fig 256

B, Projection drawing ($\times 150$) of a comparable area from a somewhat older embryo (University of Michigan Coll, EH 15, C-R, 30 mm) Note appearance of primordium of enamel organ of the milk tooth as a local bud on the side of the dental ledge

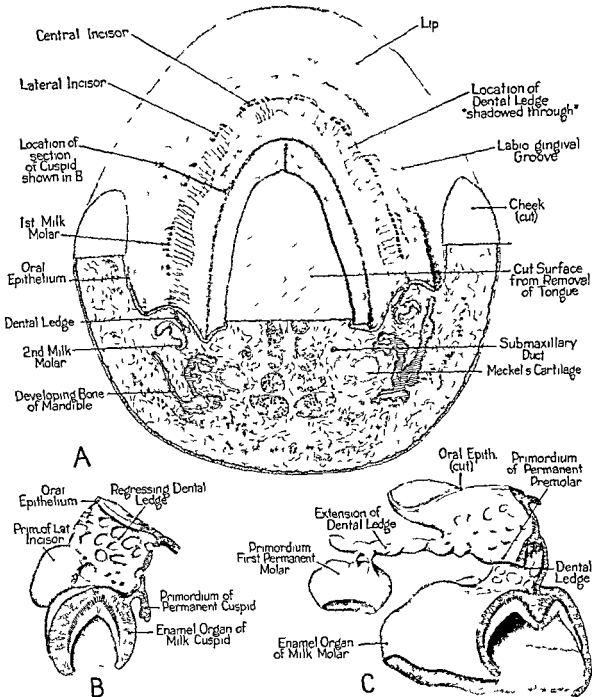


FIG 258 Schematic diagrams showing relations of enamel organs to dental ledge (Based, in part, on the reconstructions of Rose)

A, Stereographic diagram of lower jaw to show location of primordia of the enamel organs of the milk teeth

B, Stereographic diagram of the enamel organs of a cuspid and the adjacent lateral incisor, at a stage somewhat more advanced than that shown in A

C, Stereographic diagram of the enamel organ of the second milk molar showing the location of the primordium of the enamel organ of the permanent biscuspid and the extension of the dental ledge from which the primordia of the enamel organs of the permanent molars arise

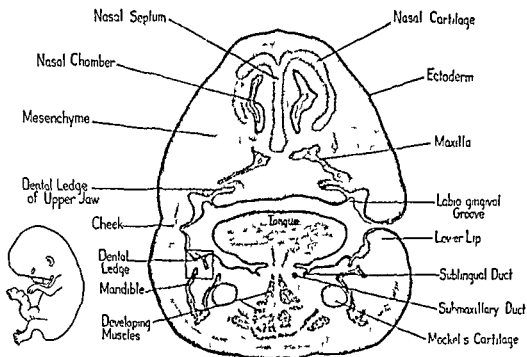


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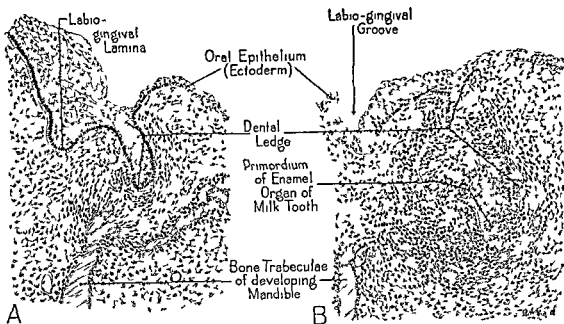


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B, Projection drawing ($\times 150$) of a comparable area from a somewhat older embryo (University of Michigan Coll., EH 15, C-R, 30 mm) Note appearance of primordium of enamel organ of the milk tooth as a local bud on the side of the dental ledge

begin to develop actively only after the jaws have enlarged sufficiently to accommodate the permanent dentition

The histogenetic processes involved in the formation of deciduous teeth and permanent teeth are essentially the same. It is, therefore, sufficient to trace them only in the case of the deciduous teeth, keeping in mind that the same process is repeated later in life in the formation of the permanent teeth. In a section of the jaw of a human embryo of the eleventh week, cut at a point

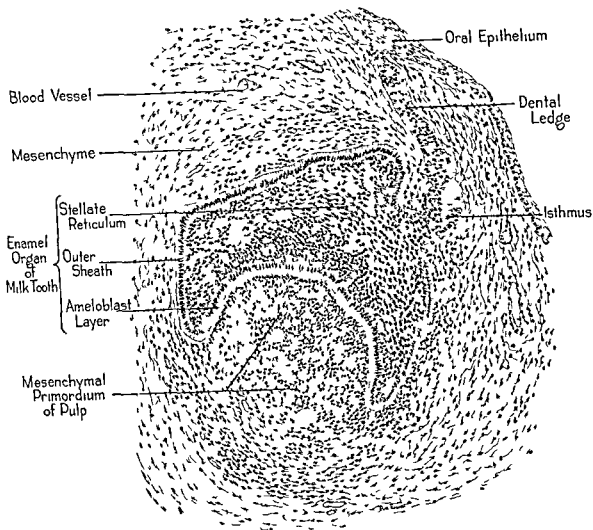


FIG 260 Projection drawing ($\times 150$) of tooth primordium in a human embryo of the eleventh week. Location of area drawn is indicated by the rectangle in Fig 259

where a "milk" tooth is developing, the shape of the enamel organ suggests that of a poorly formed, inverted goblet with the section of the dental ledge appearing somewhat like a distorted stem (Fig 260). The epithelial cells lining the inside of the goblet early take on a columnar shape. Because they constitute the layer which secretes the enamel cap of the tooth, they are called ameloblasts (enamel formers). The outer layer of the enamel organ is made up of closely packed cells which are at first polyhedral in shape but which soon, with the rapid growth of the enamel organ, become flattened. They constitute the so-called outer epithelium of the enamel organ. Between the

Dental Ledge Local changes leading toward tooth formation can be made out in the embryonic jaws toward the close of the second month of development. By the seventh week a definite thickening of the oral epithelium can be made out on both the upper and the lower jaw. This band of epithelial cells which by the eighth week has begun to push into the underlying mesenchyme around the entire arc of each jaw is known as the dental ledge (lamina) (Figs 256, 257, A). Almost coincidentally a cellular ingrowth slightly

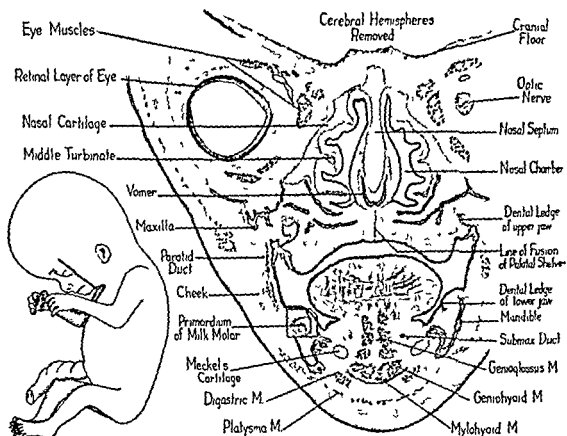


FIG 259 Projection drawing, $\times 10$, of a section through the jaws of a human embryo of the eleventh week (University of Michigan Coll., EH 198, C-R, 58 mm). Outline, left, shows actual size of embryo, and line across the jaws gives location of section. Small polygon enclosing primordium of milk molar indicates area represented at higher magnification in Fig 260.

nearer the outside of the jaw begins to mark off the territory which is to become the lip from that which is to become the gum. This bandlike ingrowth of cells is known as the labiogingival lamina (Fig 257, A).

Enamel Organs After the dental ledge is established, local buds arise from it at each point where a tooth is destined to be formed (Fig 258). Since these cell masses give rise to the enamel crown of the tooth they are termed "enamel organs." As would be expected, the enamel organs for the deciduous ("milk") teeth are budded off from the dental ledge first, but the cell clusters which give rise to the enamel of the permanent teeth, although they arise later, are formed at a surprisingly early time (Figs 258, B, C, 261). They remain dormant, however, during the growth of the deciduous teeth and

blasts to the neighboring vascular supply would appear to be significant, since it is precisely here at the tip of the crown where the ameloblasts first begin to secrete enamel (Fig 263)

By this time the dental ledge has lost its connection with the oral epithelium although traces of it can still be identified in the mesenchyme at the lingual side of the tooth germ (Fig 263) The cluster of cells which is destined to give rise to the enamel organ of the permanent tooth of this level can be seen budding off from the ledge close to the point from which the enamel organ of the milk tooth arose (Fig 261)

Formation of Dentine With these preparatory developments complete, the tooth-forming structures are, so to speak, ready to go about the fabrication of dentine and enamel As is the case with bone, enamel and dentine are both

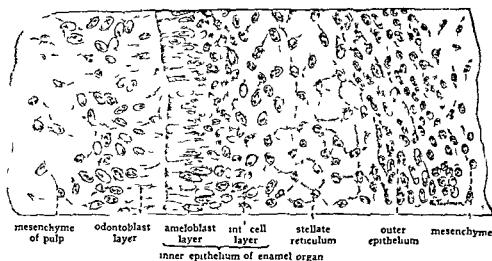


FIG 262 Projection drawing ($\times 350$) of segment of enamel organ and adjacent pulp from a 120-mm pig embryo to show ameloblast and odontoblast layers The stage of differentiation here shown is closely comparable with that seen in human embryos of the fourth month

composed of an organic basis in which inorganic compounds are deposited We may use the same comparison that was used in describing bone—that of the familiar use in construction operations of a steel meshwork into which concrete is poured, the steel giving the finished structure some degree of elasticity and increasing the tensile strength, while the concrete gives body and solidity So, likewise, in the case of such hard structures in the body as bone, dentine, and enamel, the interlacing organic strands in the matrix give the tissue its tensile strength and resilience, and the calcareous compounds deposited in the organic framework give form and hardness

Although bone, dentine, and enamel are similar in having both organic and inorganic constituents in their matrix they are quite different in detail, both as to composition and microscopical structure Bone has approximately 45 per cent of organic material while dentine has but 28 to 30 per cent, and adult enamel less than 5 per cent There are also minor differences in the kind and proportions of inorganic compounds present in each Histologically they are totally unlike Bone matrix has cells scattered through it in lacunae

outer epithelium and the ameloblast layer is a loosely aggregated mass of cells designated collectively, because of their characteristic appearance, the enamel pulp, or the stellate reticulum

Dental Papilla Inside the goblet-shaped enamel organ there is a mass of mesenchymal cells called the dental papilla. The dental papilla constitutes the primordium of the pulp of the tooth (Fig. 260). The cells of the dental papilla proliferate rapidly and soon form a very dense aggregation. A little later in development the enamel organ begins to assume the shape character-

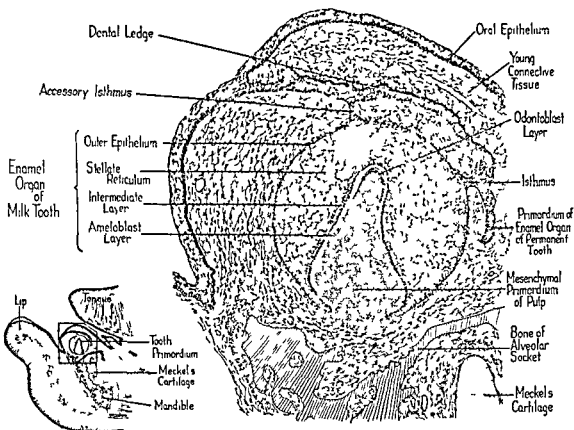


FIG. 261 Projection drawing, $\times 50$, of a parasagittal section of the lower jaw of a human embryo of the fourteenth week, passing through the primordium of a lower central incisor (University of Michigan Coll., EH 145, C-R, 104 mm). The small sketch, lower left, indicates the relations of the area represented.

istic of the crown of the tooth it is to lay down (Fig. 261). At the same time the outer cells of the dental papilla take on a columnar form similar to that of the ameloblasts (Fig. 262). They are now called odontoblasts (dentine formers) because they are about to become active in secreting the dentine.

In the central portion of the dental papilla vessels and nerves are beginning to make their appearance so that the picture is already suggestive of the condition seen in the pulp of an adult tooth. Meanwhile the growth of the dental papilla toward the gum has begun to crowd in on the stellate reticulum of the enamel organ in the region of the future tooth's crown (Fig. 261). This brings the ameloblasts of this region much closer to the many small blood vessels which lie in the surrounding mesenchyme. The approach of the amelo-

If attention is turned now to the recently formed dentine, two zones distinctly different in staining reaction can be seen. The zone nearer the cells is pale, taking but little stain (Fig. 264). This zone consists of the recently deposited organic part of the matrix not as yet impregnated with calcareous material. The zone nearer the enamel organ will be found, by contrast, very intensely stained. This is the older part of the dentine matrix which has had the organic framework¹ impregnated with calcareous material.

As the odontoblasts continue to secrete additional dentine matrix, the accumulation of their own product inevitably forces the cell layer back, away from the material previously deposited. Apparently strands of their cytoplasm

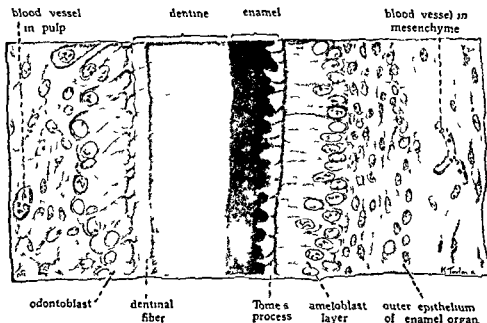


FIG. 264 Projection drawing ($\times 350$) of small segment of developing incisor from 130-mm pig embryo to show formation of enamel and dentine. The conditions here shown are closely comparable with those seen in human embryos late in the fifth month.

become embedded in the material first laid down and are then pulled out to form the characteristic processes of the odontoblasts known as the dentinal fibers (Fig. 264). As the layer of secreted material becomes thicker and the cells are forced farther from the material first deposited, these dentinal fibers become progressively longer. Even in adult teeth, where the dentine may be as much as 3 mm in thickness, they extend from the odontoblasts which line the pulp chamber to the very outer part of the dentine. These dentinal fibers are believed to be concerned with maintaining the organic portion of the

¹ There is some division of opinion among histologists as to the origin of the organic framework of dentine. It used to be thought that the odontoblasts first formed this feltlike framework of fibrous material and then impregnated it with calcium salts. Of late there has been strong advocacy of the view that the fibrous material is formed by mesenchymal cells lying close against the odontoblasts and insinuating slender processes between them. According to this interpretation the fibrous feltwork is formed through the medium of these slender cell processes and the odontoblasts are concerned only with the transfer of calcareous material. Such controversies as to details should not be allowed to divert attention from the fundamental fact that the matrix of dentine, like the matrix of bone, is formed by calcareous impregnation of a feltwork of fibers laid down in advance.

Dentine has its cellular elements lying against one face and sending long processes into tubules in the matrix. Enamel is prismatic in structure and the cells which formed it are destroyed in the eruption of the tooth.

The first dentine is deposited against the inner face of the enamel organ, the odontoblasts drawing their raw materials from the small vessels in the pulp and secreting their finished product toward the enamel organ. It is significant in this connection that in an active odontoblast the nucleus, which is the

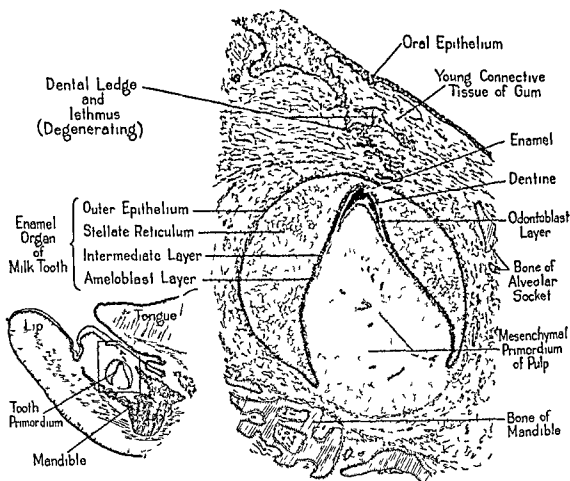


FIG 263 Projection drawing, $\times 40$ (orienting sketch, lower left, $\times 5$), of primordium of lower central milk incisor from a human embryo of 19 weeks presumptive fertilization age (University of Michigan Coll, EH 143, C-R, 174 mm)

metabolic center of the cell, gravitates toward the source of supplies and comes to lie in the extreme pulpal end of the cell (Fig 264). Significant, also, in the same connection is the fact that the end of the odontoblast toward the enamel organ, where the elaborated product of the cell is being accumulated preparatory to its extrusion, can be seen to take the stain especially intensely. Although our knowledge of intracellular chemistry is as yet exceedingly fragmentary and we do not know the exact chemical nature of the product in this stage, the staining reaction of the odontoblasts is clearly indicative of the presence of calcium compounds of some sort.

must move closer to the surface of the gum. Even when the crown of the tooth begins to erupt the root is still incomplete and it does not acquire its full length until the crown has entirely emerged.

A record of the successive zones involved in the process of calcification appears in adult teeth, in both the enamel and the dentine, in the form of the so-called contour lines or growth lines (Fig. 267). These lines, due to the cyclic variations in the rate or character of deposition, give us an unequivocal picture of the successive shapes that the tooth assumed at different stages in

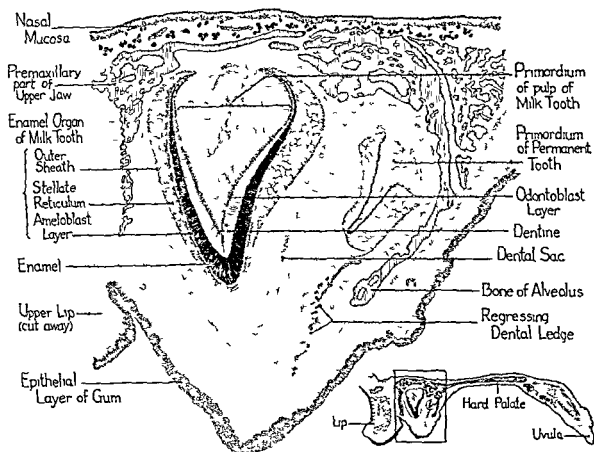


FIG. 265 Projection drawing ($\times 8$) of upper jaw of a term fetus showing developing central incisor tooth. Orienting sketch in lower right-hand corner is actual size.

its development. (Compare the extent of the enamel and the dentine as shown in Fig. 263 with the growth lines numbered 1 in Fig. 267. For a later stage in the process compare Fig. 265 with the growth lines numbered 5 in Fig. 267.)

Formation of Cementum The hard substance of a tooth known as cementum is virtually a bone encrustation of the root. No cementum is formed until the tooth has acquired nearly its full growth and approximately its definitive position in the jaw, but the first indications of specialization in the tissue destined to give rise to it can be seen long before the cementum itself appears. Outside the entire tooth germ, between it and the developing bone of the jaw, there occurs a definite concentration of mesenchyme. The concentration becomes evident first at the base of the dental papilla and extends thence crownward about the developing tooth, which it eventually completely

dentine matrix in a healthy condition. When the pulp is removed from a tooth, taking with it the odontoblasts, we know that the dentine undergoes degenerative changes which involve, among other things, darkening and increase in brittleness. This would seem to be attributable to the degeneration of the organic framework of a matrix no longer nourished by the odontoblasts. It is also probable that these slender cytoplasmic processes act as intermediaries in transmitting pain impulses to the nerve fibers which end about the base of the odontoblasts.

Formation of Enamel While the dentine is being laid down by the cells of the odontoblast layer, the enamel cap of the tooth is being formed by the ameloblast layer of the enamel organ. As was the case with the odontoblasts the active cells of the ameloblast layer are columnar in shape, and their nuclei, too, lie in the ends of the cells toward the source of supplies—in this case the small vessels in the adjacent mesenchyme (Fig. 264). The amount of organic material laid down as the framework of enamel is much less than is the case with either bone or dentine, and consequently it is rather more difficult to make out its precise character and arrangement. It is, nevertheless, possible to see in decalcified sections, delicate fibrous strands projecting from the tips of the ameloblasts into the areas of newly formed enamel (Fig. 264). It seems probable that these strands (Tomes fibers or processes) are in some way involved in the formation of the organic matrix of enamel. The problem of tracing the relations of Tomes fibers is greatly complicated by the fact that, where the ameloblasts have deposited calcium compounds, the calcium has rendered the organic part of the matrix so avid in its affinity for stains that it is not possible to discern fine structural details because of the very density of the resulting coloration (Fig. 264). This reaction of the tissue to stains persists even after the inorganic calcium compounds have been removed by decalcification, indicating that the organic framework itself has been chemically altered by the calcium deposited in it.

In spite of these difficulties in getting at the exact nature and arrangement of the organic matrix of enamel, it is quite possible to see the genesis of its fundamental prismatic structure. Each ameloblast builds up beneath itself a minute rod or prism of calcareous material. These prisms are placed with their long axes approximately at right angles to the dento-enamel junction. Collectively they form an exceedingly hard cap over the crown of the tooth which in its structural arrangement suggests a paving of polygonal bricks laid on end. There is sufficient difference in the rate at which the different ameloblasts work so that in actively growing enamel the surface is jagged and irregular, due to the varying extent to which the different prismatic elements have been calcified (Fig. 264).

Enamel formation and dentine formation both begin at the tip of the crown (Fig. 263) and progress toward the root of the tooth. The entire crown is well formed before the root is much more than begun (Fig. 265). The progressive increase in the length of the root is an important factor in the eruption of the tooth, for as the root increases in length the previously formed crown

must move closer to the surface of the gum. Even when the crown of the tooth begins to erupt the root is still incomplete and it does not acquire its full length until the crown has entirely emerged.

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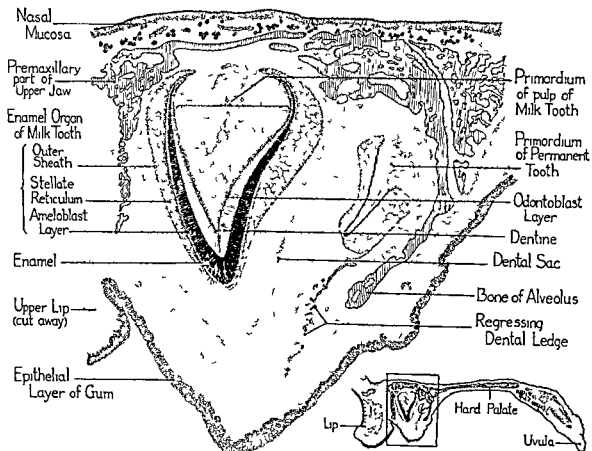


FIG 265 Projection drawing ($\times 8$) of upper jaw of a term fetus showing developing central incisor tooth. Orienting sketch in lower right-hand corner is actual size.

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surrounds. This mesenchymal investment is known as the dental sac (Fig 265). In the eruption of the tooth the portion of the dental sac over the crown is destroyed, but the deeper portion of the sac persists and becomes differentiated into a connective-tissue layer which is closely applied about the dentine of the growing root. This layer in its origin from mesenchyme, and in

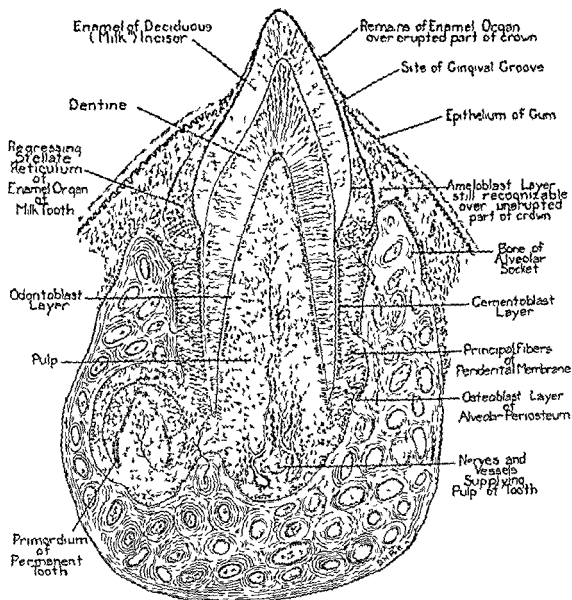


FIG. 266 Semischematic diagram showing a milk tooth partially erupted. The root is not yet fully formed, but the arrangement of tissues surrounding growing root already indicates how it will be attached within alveolar socket.

the manner in which it becomes specialized, closely resembles the periosteal layer about a developing bone. It is to all intents and purposes a layer of periosteal tissue with its osteogenetic cells next to the root of the tooth and its fibrous layer merging with the periosteal layer lining the alveolar socket. These two periosteal layers lying, so to speak, back to back in the space between the tooth and the bone of the jaw together constitute the *periodontal membrane*. Because the cells of the periodontal membrane adjacent to the tooth form

cementum, they are said to constitute the *cementoblast layer* (Fig 266) At about the time the tooth has acquired its final position in the jaw the cells of this layer begin to deposit cementum about the dentine of the root Histologically and chemically, as one might expect from its manner of origin, cementum is very similar to subperiosteal bone At first thin, the layer of cementum is gradually thickened as the tooth matures

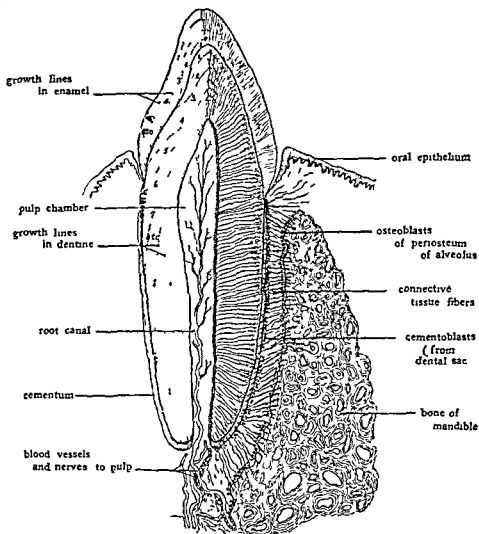


FIG 267 Schematic diagram showing topography of a tooth and its relations to the bone of the jaw. Numbered zones indicate empirically the sequence of deposition of dentine and enamel. The so-called growth lines in dentine and enamel follow general contours indicated by dotted lines in illustration but are much more numerous.

Attachment of the Tooth in the Jaw The attachment of the tooth is brought about by the development of strong bundles of white fibrous connective tissue in the periodontal membrane between its root and the bony socket in which it lies. As the periosteum of the alveolus adds new lamellae of bone to the jaw on the one side, and the cementoblasts add lamellae of cementum to the root of the tooth on the other, the ends of these fiber bundles in the alveolar periosteum are caught in the new lamellae. Thus the tooth comes to be held in place by fibers which are literally calcified into the cementum of the tooth at one end, and into the bone of the jaw at the other.

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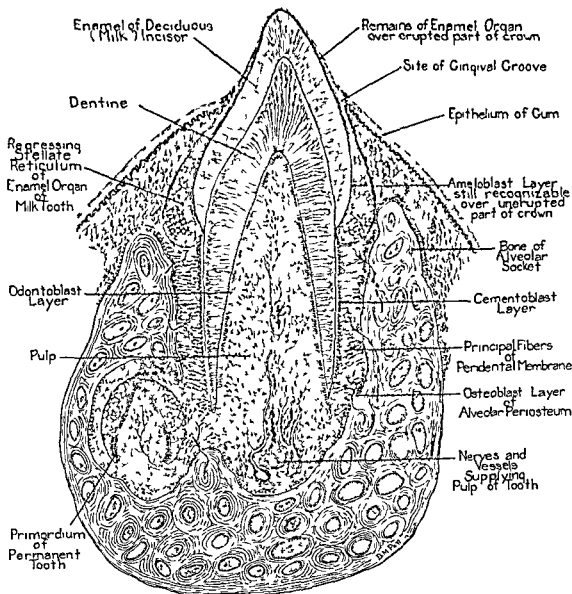


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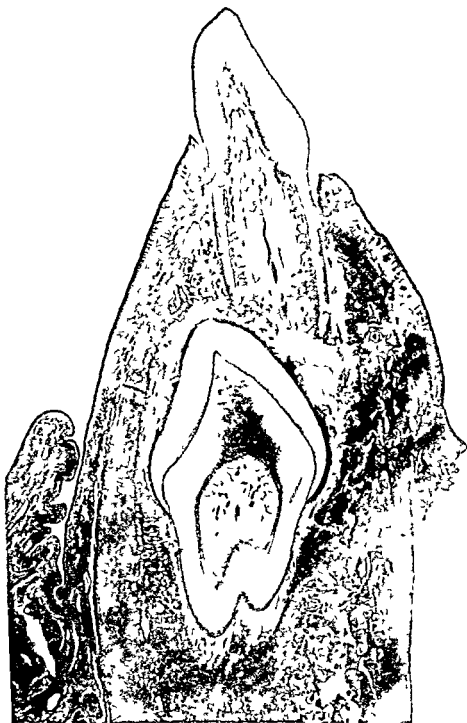


FIG 269 Photomicrograph ($\times 6$) of section through jaw of a puppy showing a milk tooth nearly ready to drop out and the developing permanent tooth deeply embedded in the jaw below it. Space about crown of permanent tooth was occupied in the living condition by enamel. Fully formed enamel, being approximately 97 per cent inorganic in composition, is almost completely destroyed by the decalcification with acids which must be carried out before such material can be sectioned. (From a preparation loaned by Dr S W Chase)

(Figs 266, 267) The mechanism involved is precisely the same as that which occurs in the burying of tendon fibers in a growing bone, where the buried ends of the fibers are known as the penetrating fibers of Sharpey.

Replacement of Deciduous Teeth by Permanent Teeth The replacement of the deciduous or "milk" dentition by the permanent teeth is a process which varies in detail for each tooth. The general course of events is, however, essentially similar in all cases. The enamel organ of the permanent tooth arises from the dental ledge near the point of origin of the corresponding milk

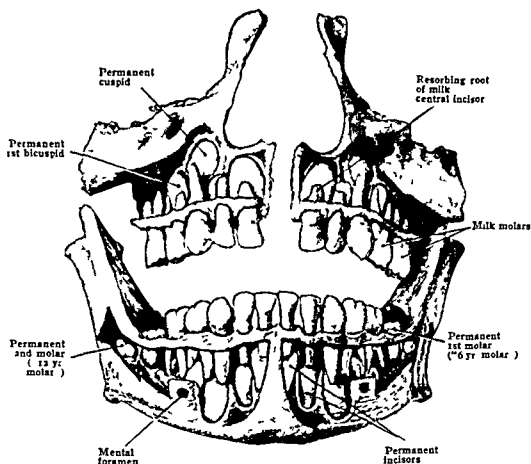


FIG. 268 Jaws of a child in sixth year dissected to show relations of primordia of permanent teeth to milk dentition (Redrawn after Broomell and Fischelis, in "Anatomy and Histology of the Mouth and Teeth")

tooth (Fig. 261). With the disappearance of the dental ledge the permanent tooth germ comes to lie in a depression of the alveolar socket on the lingual side of the developing milk tooth (Fig. 265).

When the jaws approach their adult size the hitherto latent primordia of the permanent teeth begin to go through the same histogenetic changes we have traced already in the case of the temporary teeth. As a permanent tooth increases in size, the root of the corresponding deciduous tooth is resorbed and the permanent tooth comes to lie underneath its remaining portion (Figs. 268, 269). Eventually nearly the entire root of the milk tooth is destroyed and its loosened crown drops out, making way for the eruption of the permanent tooth.

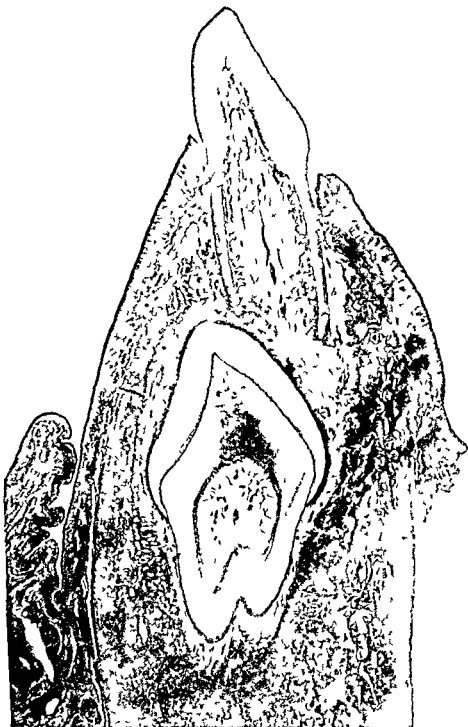


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In the foregoing pages the development of the teeth has been presented in general terms with the emphasis on interpreting the fundamental histogenetic processes involved. Because of the simplicity of their configuration incisor or cuspid (canine) teeth have been used for illustrative purposes. With minor modifications as to details the account is applicable to the development of more complex teeth such as the bicuspid or molars. It is only necessary to realize that in the formation of a tooth with multiple cusps and roots the enamel organ is shaped accordingly. The growth of each cusp and each root of a molar proceeds along the same lines followed by the single crown and single root of an incisor.

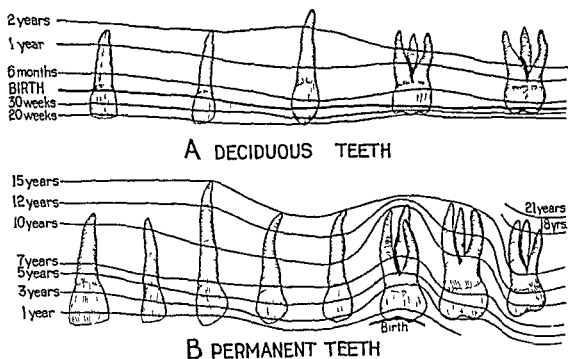


FIG. 270 Progress of calcification in deciduous and permanent teeth (Adapted from several sources)

Times of Calcification and of Eruption Each type of tooth in the deciduous dentition and the permanent dentition has its individual history as to the time calcification begins and the time eruption may be expected. There is, of course, considerable variability, but the approximate ages at which these events occur in the different teeth is fairly well established. Fig. 270 summarizes graphically the data on the rate of calcification. Where a time line crosses the diagram of a tooth, it indicates that the portion of the tooth crownward from the line has been calcified at that time. The accompanying table gives the ages at which the eruption of the different teeth may be expected. It should be emphasized that these are merely the usual ages and that considerable individual variation may be expected to occur within the range of normalcy. The information covered by the calcification graph of Fig. 270 and the following table on tooth eruption is of the type that should be available for ready reference. Unless one were working in a field such as pediatrics,

radiology, or orthodontia, where such information is regularly utilized, its memorizing would not be a profitable use of one's time and energy

TABLE SHOWING USUAL AGES AT WHICH ERUPTION OF THE DIFFERENT TEETH MAY BE EXPECTED TO OCCUR

<i>Deciduous Teeth</i>		<i>Permanent Teeth</i>	
Central incisors	6-8 mos	Central incisors	about 7 yrs
Lateral incisors	7-10 mos	Lateral incisors	8-9 yrs
Cuspids	14-18 mos	Cuspids	12-13 yrs
First molars	12-14 mos	First bicuspid	about 10 yrs
Second molars	20-24 mos	Second bicuspid	about 11 yrs
		First molars	6-7 yrs
		Second molars	12-13 yrs
		Third molars	17-25 yrs and sometimes much later

Developmental Abnormalities of the Teeth The common developmental disturbances in tooth formation may involve defective laying down of their hard substances, abnormalities in the shape of individual teeth and abnormalities in the number and position of the teeth within the jaws

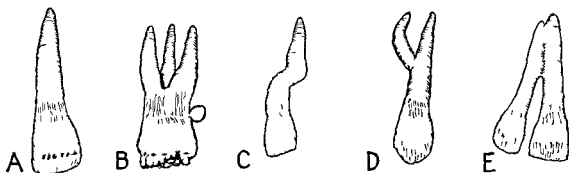


FIG 271 Developmental anomalies of teeth (Schematized from cases illustrated in Endleman and Wagner "General and Dental Pathology" A, Upper central incisor with row of erosion pits along outcrop of a zone of hypoplastic enamel B, First molar with so-called "raspberry crown" due to hypoplastic enamel Same tooth shows an "enamel pearl" adherent to its neck C, Upper lateral incisor showing changes in direction of growth during root formation D, Cuspid showing abnormal root bifurcation E, Upper central and lateral incisors with their roots grown together

CALCIFICATION DEFECTS Calcification defects may involve any of the hard parts of a tooth and their nature is correlated with the structural pattern and the manner of development of the part involved The commonest defect in enamel formation is due to disturbances in calcium deposition Such hypoplasia of the enamel often shows up along the outcrop of a particular growth line It may be indicated merely by a band of opaque whiteness if the deficiency in calcification is slight, or if it is more extreme a row of erosion pits is likely to show at the surface (Fig 271, A) By reference to the calcification chart (Fig 270), one can ascertain the time at which the defective growth occurred For example, the zone of defective enamel in the upper central incisor shown in Fig 271, A, must have been laid down in the unerupted tooth when the child was about a year old The number of instances in which

some acute illness, especially one involving cutaneous eruptions and marked temperature elevation, occurred at the time the defective enamel was being formed, strongly suggests a causal relation. This is borne out by the appearance of calcification defects in the corresponding age zones of other teeth (See, for example, the first molar shown in Fig. 271, B).

In the dentine defective calcification most often occurs in the form of multiple small areas (interglobular spaces) in which calcium was not deposited. Such spaces may be so small and scattered that they have little practical importance, or they may be so extensive in some particular growth zone that they constitute a line of structural weakness in the tooth.

ABNORMALITIES IN SHAPE OF INDIVIDUAL TEETH These are not uncommon. There may be sharp bends in the root indicating some disturbance in the relations of the root sheath (Fig. 271, C). In extreme cases the root may even recurve so it is hook-shaped. A tooth which ordinarily shows but a single root may have one which is bifurcated (Fig. 271, D). Conversely, a molar tooth which normally shows three roots may have them run together as a single ill-shaped mass. Occasionally the roots of two adjacent teeth may impinge on each other and grow together (Fig. 271, E).

ENAMEL PEARLS Enamel pearls are curious spheroidal masses of enamel, which may appear adherent to a tooth or free in the adjacent connective tissue. One of the commonest sites for an enamel pearl is adherent to the neck of a tooth (Fig. 271, B). In this location it is formed by an aberrant vesicle of ameloblasts associated with the enamel organ which forms the crown of the tooth involved. When enamel pearls appear in the surrounding connective tissue it is believed that they are derived from a vesicle of ameloblasts formed from remnants of the dental ledge, which of course contains cells of ameloblastic potentialities.

ABNORMALITIES IN NUMBER OF TEETH Not infrequently there may be supernumerary teeth formed, such as an additional incisor or a fourth molar. More common than the presence of such extra teeth not characteristic of the human dentition are instances in which one or more teeth fail to form. Such agenesis is most likely to occur in the case of the third molars. Instances have been reported in which an individual never developed any teeth of either deciduous or permanent dentition. Really complete anodontia is exceedingly rare, even among anomalies. When it does appear it is associated with a profound dysplasia of all the specialized ectodermal derivatives such as hair, fingernails, and cutaneous glands.

From time to time reports of a third dentition appear. In all probability such late-appearing teeth do not represent a third dentition. It would seem more likely that they are teeth of the permanent dentition—perhaps supernumerary ones—that have remained for years unerupted and finally put in a belated appearance.

ABNORMALITIES IN ARRANGEMENT OF TEETH IN THE JAW Irregularities of tooth arrangement are of very common occurrence. There is apparently a very delicate balance between the size of the jaws and the space necessary to

accommodate the permanent dentition, and our composite heredity may bring large teeth from one ancestor and small jaws from another. During the growth period a surprisingly small stimulus—even the slight pressure exerted by the familiar orthodontic brace on overcrowded teeth—is effective in causing the bone of the jaw to adapt its growth in response to the pressures applied. The usual malpositions of the teeth are relatively slight and are readily remediable by appropriate orthodontic procedures instituted at the proper time and continued sufficiently long. There are occasional cases in which teeth appear as far out of their proper location as the palate, or the base of the gum on its labial face.

Development of the Digestive and Respiratory Systems

DIGESTIVE TUBE

In considering the structure of young embryos, we saw the walling in of the primitive gut by splanchnopleure and its early division into an extra-embryonic portion, the yolk-sac, and an intra-embryonic portion destined to form the gastro-intestinal tract (Fig 70, A, B) We traced also the primary regional division of the intra-embryonic gut into foregut, midgut, and hindgut, and the establishment of the oral and anal openings by the breaking through of the stomodaeal depression cephalically and the proctodaeal depression caudally (Figs 57, 70, C, D) At the end of the first month of development, local differentiations in the gut tract already foreshadow the development of certain organs and give indications of the impending establishment of others Starting with these now familiar conditions as a basis, we shall trace briefly the more important steps by which the adult structure and relations of the various digestive organs are established Although the oral region is, of course, part of the digestive system, its differentiation is so closely related to the formation of the face that it was expedient to deal with it in that association in the preceding chapter We may now, therefore, logically turn our attention to that part of the gut tract which lies directly behind the oral region

Pharyngeal Region In embryos entering their second month, the cephalic part of the foregut has become differentiated as the pharynx Greatly compressed dorsoventrally, the pharynx has a wide lateral extent with a series of pouchlike diverticula pushing out on either side between the visceral arches (Fig 251) This stage of the pharynx is a recapitulation of conditions which had an obvious functional significance in water-living ancestral forms, the pharyngeal pouches of the mammalian embryo being homologous with the inner portion of the gill slits The repetition of race history is here, as so frequently happens, slurred over Although in the mammalian embryos the tissue closing the gill clefts becomes reduced to a thin membrane consisting of nothing but a layer of entoderm and ectoderm with no intervening mesoderm, this membrane rarely disappears altogether Occasionally the more cephalic of the pharyngeal pouches break through to the outside, establishing open gill slits, but in such cases the opening is usually short-lived and the clefts promptly close again

Like many other vestigial structures which appear in the development of higher forms, the pharyngeal pouches give rise to organs having a totally different functional significance from the ancestral structures they represent. It is as if, to speak figuratively, nature was too economical to discard entirely structures rendered functionally obsolete by the progress of evolution, but rather conserved them, in part at least, and modified them to carry on new activities. While they might logically be discussed here, the processes involved in converting local evaginations of the original pharyngeal pouches into endocrine glands such as the parathyroids, can be considered more conveniently when we take up the ductless glands as a group (Chapter 17).

The main pharyngeal chamber of the embryo, that is the central portion in distinction to its various diverticula, becomes converted directly into the pharynx of the adult. In this process its lumen is simplified in configuration and relatively reduced in extent. The first pair of pharyngeal pouches, extending between the mandibular and hyoid arches, come into close relation at their distal ends with the auditory vesicles (Fig. 243). These pouches give rise, on either side, to the tympanic cavity and to the Eustachian tube in a manner which already has been discussed in connection with the development of the ear. The second pair of pouches are largely absorbed into the pharyngeal wall. They take part in the formation of the tonsillar region and supratorsillar fossae (Fig. 328).

The third and fourth pairs of pouches give off outgrowths which take part in the formation of a group of ductless glands—the parathyroids, thymus, and postbranchial bodies. After the migration of these primordia into the adjacent mesenchyme the remains of the original pouches are reduced rapidly in extent and give rise only to local depressions in the pharyngeal wall adjacent to the pharyngopalatine (pharyngo-epiglottic) fold (Fig. 328).

Esophagus Caudal to the level of the visceral pouches the pharynx becomes abruptly narrowed in its lateral extent. It is just cephalic to this point of transition, at the level of the fourth pouches, that the pharynx gives rise ventrally to the tracheal outgrowth (Figs. 56, 70, D). The region where the trachea becomes confluent with the gut tract is therefore derived from the most posterior part of the embryonic pharynx. From this point to the dilation which marks the beginning of the stomach, the gut remains of relatively small and uniform diameter and becomes the esophagus. The esophagus is at first very short (Fig. 272), but later in development, as the stomach moves caudad in the body from its place of origin, the esophagus becomes much longer (Figs. 273, 274).

Stomach The region of the primitive gut which is destined to become the stomach is indicated as early as the end of the fourth week by a slight local dilation (Fig. 70, D). By six weeks its shape is strikingly suggestive of that of the adult stomach. Its position is, however, quite different. In young embryos the stomach is mesially placed with its cardiac (esophageal) end somewhat more dorsal in position than its pyloric (intestinal) end (Fig. 308).

It is slightly curved in shape, with the convexity facing dorsally and somewhat caudally

The positional changes by which it reaches its adult relations involve three principal phases (1) The stomach is shifted in position so its long axis no longer lies in the sagittal plane of the embryo but diagonally across it,

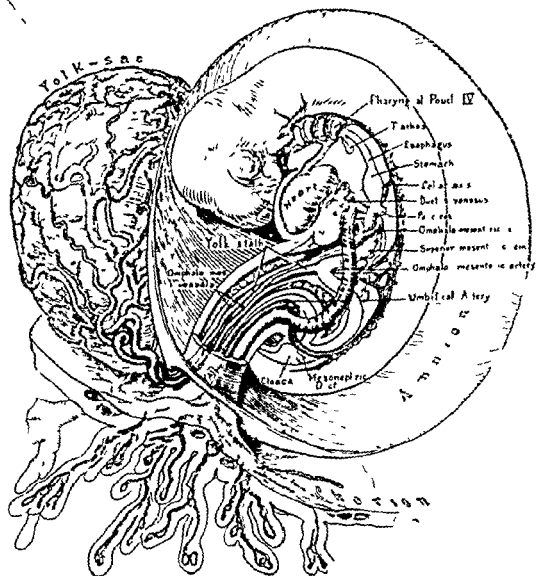


FIG 272 Gut tract of a human embryo of 5 mm (From a drawing by Brodel in Cullen "Embryology, Anatomy and Diseases of the Umbilicus," courtesy, W B Saunders Co)

(2) there is a concomitant rotation of the stomach about its own long axis so that its original dorsoventral relations are altered, and (3) the stomach during its axial and rotational changes is carried farther caudad in the body. The first two phases of these changes are schematically indicated in Fig 275. The shift in axis takes place in such a manner that the cardiac end of the stomach comes to lie to the left of the mid-line and the pyloric end to the right. Meanwhile rotation has been going on. In following the progress of rotation the best point of orientation is the line of attachment of the dorsal

mesentery, which is primarily mid-dorsal, along what is destined to be the greater (convex) curvature of the stomach (Figs 308, 309) As the stomach continues to grow in size and depart from the sagittal plane of the body, it rotates about its own long axis The convex surface to which the dorsal mesentery is attached, and which was at first directed mid-dorsally, now swings to the left Since the long axis itself has in the meantime been acquiring an inclination, the greater curvature of the stomach comes to be directed

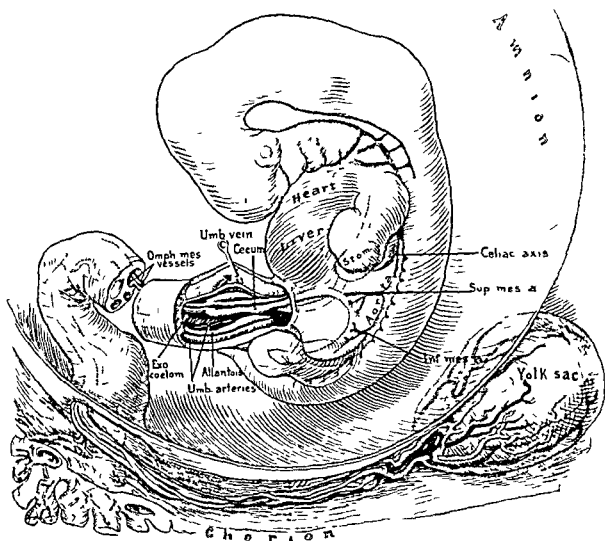


FIG 273 Gut tract of a human embryo of 10 mm (From a drawing by Brodel in Cullen "Embryology, Anatomy and Diseases of the Umbilicus," courtesy, W B Saunders Co)

somewhat caudally as well as to the left (Fig 275, C, D) The change in position of the stomach necessarily involves changes in that part (dorsal mesogastrium) of the primary dorsal mesentery which suspends it in the body cavity The dorsal mesogastrium is pulled after the stomach and forms a pouch known as the omental bursa (Fig 275), the relations of which we shall have occasion to return to in the next chapter where the mesenteries are discussed in more detail

While the stomach is rotating and changing its axial position, it is at the same time gradually being carried to a more caudal position in the developing

body. At the end of the first month, when the dilation of the part of the gut which is to be the stomach is just beginning to become recognizable, it is located immediately dorsal to the heart (Fig. 272). During the second month

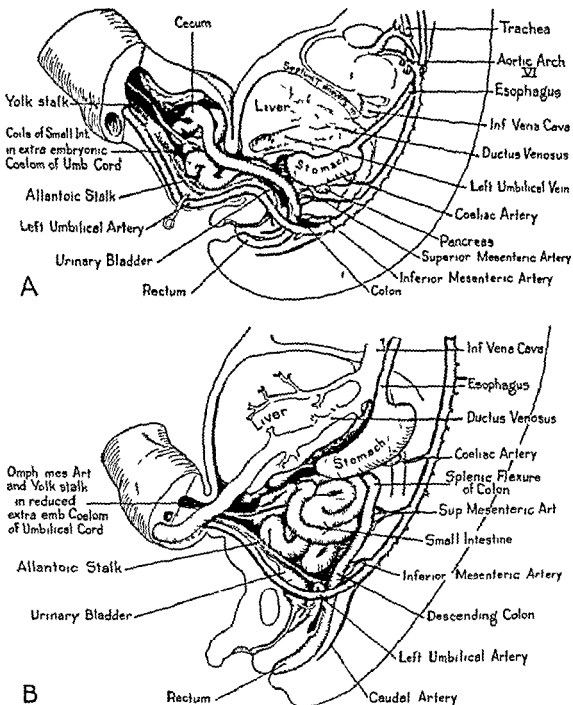


FIG. 274 Withdrawal of gut from umbilical cord (Redrawn with some modifications from illustrations by Brodel in Cullen "Embryology, Anatomy and Diseases of the Umbilicus," courtesy, W. B. Saunders Co.) A, Before retraction, in an embryo of 23 mm. B, After retraction, in an embryo of 45 mm.

the stomach moves from this level well down into the abdominal part of the body cavity (Figs. 273, 274). This of course involves a very rapid increase in the length of the esophagus. It also determines a characteristic descending

course for the associated visceral branch of the vagus nerve. The gastric branches of the vagus, having established their relations with the stomach when it was far forward in its primitive position, follow along with it in its caudal migration.

Intestines At the end of the first month of development, the intestines are represented by that part of the primitive gut tube which extends from the stomach to the cloaca. The entire intestinal tract at this stage lies in the sagittal plane of the body and follows fairly closely parallel to the curvature of the developing neural tube (Fig 70, D). The first conspicuous departure from this condition is due to the rapid elongation of the gut which begins during the fifth week. This results in the formation of a hairpin-shaped loop in the gut which extends ventrally into the belly-stalk (Figs 272, 273). The

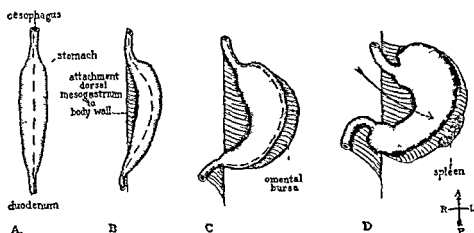


FIG 275 Diagrams illustrating changes in position of the stomach, and formation of the omental bursa. Broken line indicates attachment of mesogastrium along that surface of the stomach which is primarily mid dorsal. Arrow passes dorsal to stomach into omental bursa.

connection of the yolk-stalk with the gut lies at the bend of the loop and forms an excellent point of orientation in following the bendings and twistings by which the definitive configuration of the intestinal tract is established. For convenience in description, the part of the gut between the stomach and the yolk-stalk is designated as the cephalic limb of the primary gut loop, and that part between the yolk-stalk and the cloaca as the caudal limb. We know from following later stages that the yolk-stalk is attached to the embryonic gut just cephalic to what will be the point of transition (ileocecal valve) from small to large intestine. Thus the cephalic limb of the gut loop is involved in forming the 18 to 20 feet of small intestine comprised by the duodenum, the jejunum, and the upper part of the ileum, and the caudal limb goes to form the terminal two to three feet of the ileum and all of the large intestine. In the cephalic limb of the primary gut loop the position of the hepatic and pancreatic diverticula from the first indicates that part of the gut which is to become the duodenum. Before the yolk-stalk disappears, a small local dilation in the caudal limb of the primary gut loop indicates where the cecum is starting to form and so gives us a new landmark indicating the exact site of

transition from small to large intestine (Fig 273) Paradoxically, the part of the gut which is to be the large intestine is at first of less diameter than the part which is to be small intestine It is not until about the fifth month that the large intestine acquires its characteristically greater diameter

The positional changes which bring about adult relationships are initiated by the throwing of a twist in the primary U-shaped bend of the gut which extends into the belly-stalk Viewing the gut tract in ventral aspect, the twist is counterclockwise (Fig 309, B, C) The immediate result of this twist is to bring a considerable proportion of the original cephalic limb of the gut loop into a position in the belly below the segment of the caudal limb which was twisted across it This initial twist is the primary factor in establishing the fundamental positional relations of the large and small intestines We can recognize immediately in the crossing segment of the caudal limb of the gut loop what we know in the adult as the transverse colon We can see, also, just how it comes about that the adult jejunum and ileum lie in the abdomen below the level of the transverse colon (Figs 274, 309)

The coiling which is so characteristic of the small intestine begins to be evident immediately after the primary twist in the gut loop has occurred That portion of the cephalic limb of the primary loop which emerges below the transverse colon is, as we have seen, destined to become jejunum and ileum This part of the intestine now begins to increase exceedingly rapidly in length and consequently becomes freely coiled on itself The coiling begins while the twisted primary gut loop still projects out into the extra-embryonic coelom of the belly-stalk, giving the embryo at this age the appearance of having an umbilical hernia (Figs 274, A, 364) By about the tenth week of development the abdomen has enlarged sufficiently to accommodate the entire intestinal tract, and the protruding part of the intestinal loop is pulled back through the umbilical ring into its definitive position within the peritoneal cavity (Fig 274, B) In this retraction the coils of small intestine tend to slip into the abdominal cavity ahead of the protruding part of the colon In so doing they crowd to the left the lower part of the colon which has remained from the first in the abdominal cavity This establishes the descending colon in its characteristic position close against the body-wall on the left (Figs 309, 313) When the upper part of the colon which projected into the belly-stalk is finally drawn into the peritoneal cavity, its cecal end swings to the right and downward This means that intestinal contents entering the colon from the small intestine must pass upward in going toward the transverse colon For this reason this segment of the large intestine is known as the ascending colon (Figs 309, 313)

Cecum and Appendix The originally inconspicuous cecal dilation, which by the sixth week indicates the point of junction of small and large intestines, is destined to undergo marked local specialization By two months changes in the position of the gut tract make the small intestine enter the large almost at right angles instead of in alignment as was the case at first At this angular junction the colon develops a diverticulum which is known as the cecum

(Fig 276, A, B) For a time the cecum as a whole continues to enlarge. By the third month, however, its distal end begins to lag behind the rest of the cecum in its growth so it appears as an extension which is definitely smaller in diameter. This slender extremity of the cecal diverticulum is the vermiform appendix (Fig 276, C-E). As is so frequently the case with phylogenetically decadent structures, it is highly variable in form and likely to be the site of pathologic involvement.

Rectum and Anus The attainment of definitive conditions at the cloacal end of the digestive tract is so intimately associated with the development of the urogenital openings that changes in this region as a whole can be taken up more profitably later, in connection with the reproductive organs.

Histogenesis of the Walls of the Digestive Tube The primary entodermal layer of the embryonic gut tract gives rise only to the epithelial lining

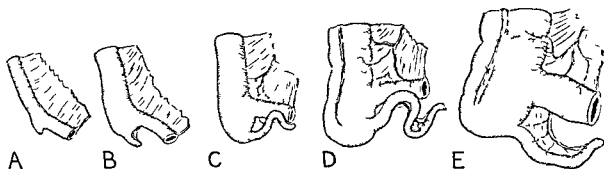


FIG 276 Semischematic sketches showing development of cecum and appendix (Adapted from a number of sources) A, Seventh week B, Ninth week C, Fourth month D, Term fetus E, Adult

and to the glands of the fully formed digestive tube. Its connective tissue and muscle coats are derived from mesenchymal cells which become aggregated about the original entodermal tube. Although each region has its own specializations, the digestive tube as a whole shows four characteristic layers. From the lumen outward these are (1) The mucosa, (2) the submucosa, (3) the tunica muscularis, and (4) the adventitia or serosa.

MUCOSA The mucosa consists of the epithelial lining, the glands developed from the epithelium, and a delicate supporting layer of connective tissue known as the tunica propria mucosae. The deepest part of the mucosa is usually a thin layer of smooth muscle called the *muscularis mucosae*, although this layer is not present in all locations.

SUBMUCOSA The submucosa is a layer of connective tissue which holds the mucosa to the main muscle layer of the gut wall. It is richly vascular and sufficiently loosely woven to permit free changes of shape as the contents of the tube vary in amount, and as the tube itself constricts or shortens with the contraction of its circular or longitudinal muscle layers. In certain locations the submucosa may contain lymph follicles or the deeper parts of glands which have grown down into it from the mucosa.

TUNICA MUSCULARIS The tunica muscularis is a robust muscle coat consisting of an inner layer of muscle elements which are circularly disposed and

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an outer layer arranged longitudinally. In the pharynx and the upper part of the esophagus this muscle is voluntary (striated). In the remainder of the tube it is involuntary (smooth).

ADVENTITIA, SEROSA Outside the tunica muscularis is a layer of connective tissue in which the vessels and nerves supplying the gut wall branch freely on their way to their local destinations. In the case of any part of the gut which does not lie free in the body cavity but is embedded in the surrounding body structures, this outer coat is called the adventitia. The connective tissue of the adventitia blends without definite line of demarcation into the adjacent connective tissue of the body. Thus, for example, the outermost coat of the wall of the esophagus which is embedded in the mediastinum would be designated as its adventitia. In the case of a part of the gut tract which lies within the body cavity, the corresponding connective-tissue layer will be supplemented by an epithelial layer derived from the mesoderm which lines the coelomic cavities (Fig. 299). This mesothelial layer provides a smooth, moist surface which permits the viscera within the body cavity to change shape and position with a minimum amount of friction. Thus the outermost coat of an organ such as the stomach would be connective tissue, corresponding to an adventitia, plus a mesothelial covering. Such a layer is designated as a serosa.

The four fundamental layers, which are common to the digestive tube as a whole, begin to be recognizable relatively early in development. As soon as the zone of mesenchyme which is destined to form the tunica muscularis becomes visibly differentiated from the mesenchyme which forms the adjacent connective-tissue layers, the topography of the gut wall can be interpreted readily in terms of the adult tunics which are taking shape (Figs. 278, 279). The histological differences in the mucosal layer which are such important distinguishing characteristics of the various adult regions of the digestive tube do not become apparent until somewhat later. Such specializations as the thick stratified squamous epithelium of the esophagus, the pits in the gastric mucosa into which the glands empty, or the villi projecting from the mucosa of the small intestine are not clearly recognizable until relatively late in development (Figs. 278, 279).

There are many curious indirections involved in these histogenetic changes. For example, the epithelium of the esophagus which is first present in the simple columnar form characteristic of the entire young entodermal lining of the gut tract (Fig. 280, A-C), goes through a transient stage of ciliation (Fig. 280, E) before it begins to acquire its final stratified squamous condition (Fig. 280, H). Similarly, the mucosa of the large intestine forms villi like those of the small intestine only to have them resorbed again in attaining its characteristic nonvillated adult condition (Fig. 281).

Meconium In the first third of intra-uterine life the intestines are devoid of solid contents. Beginning with the fourth month an increasing amount of material accumulates in their lumen. This material, called meconium, is heterogeneous in origin, consisting of a mixture of cast-off epithelial cells,

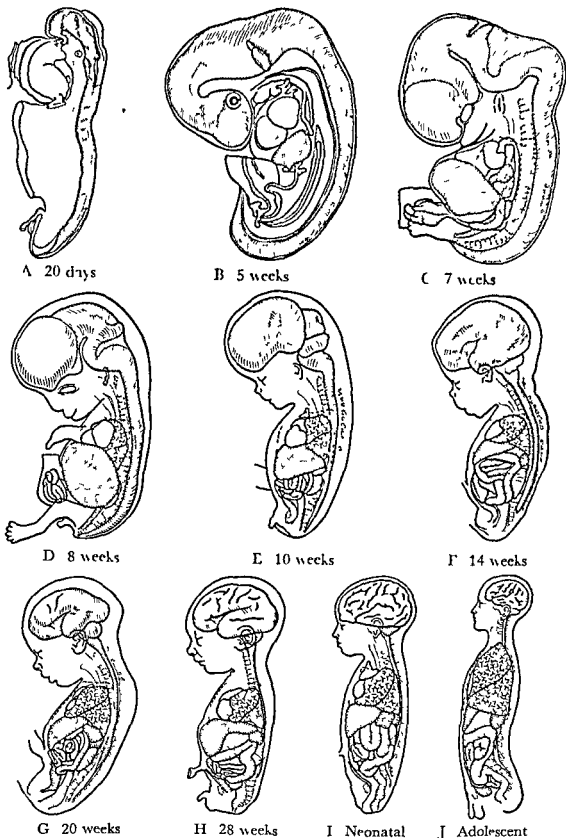


FIG 277 Semischematic diagrams graphically summarizing some of the main steps in the pre- and postnatal development of the digestive system. To facilitate comparisons, body length has been held constant and the viscera drawn to proper proportions within the body outlines (Ten stages selected from the Scammon-Lewis series in Morris "Human Anatomy")

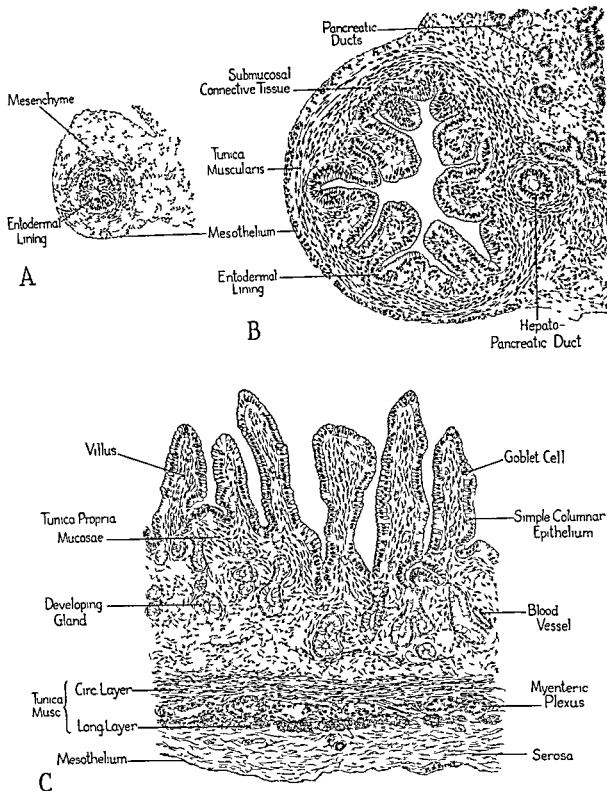


FIG. 279 Three stages in histogenesis of small intestine. Projection drawings, $\times 100$, from University of Michigan series. A, From an embryo of the sixth week (10 mm). B, From an embryo of the eighth week (25 mm). C, From an embryo of 19 weeks (174 mm).

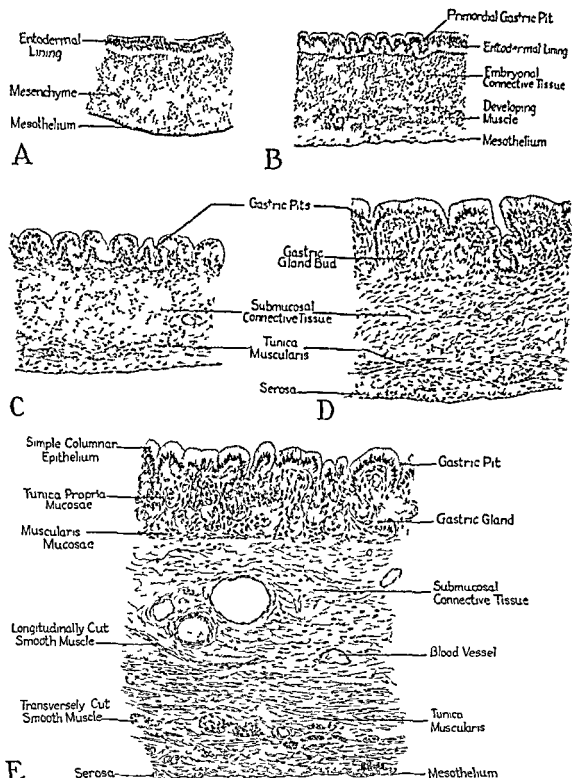


FIG 278 Histogenesis of layers in wall of stomach. Projection drawings ($\times 100$) from University of Michigan series of human embryos. A, At 10 mm; B, At 25 mm; C, At 65 mm; D, At 104 mm; E, At six months.

is known as a *stenosis*. When the narrowing goes to the point of complete obliteration of the lumen, the condition is called *atresia*. These terms alone do not imply anything as to the causation of the condition they characterize. Either a stenosis or an atresia may be developed postnatally as a sequel to tissue injury. For example, a child who has swallowed a caustic poison, such

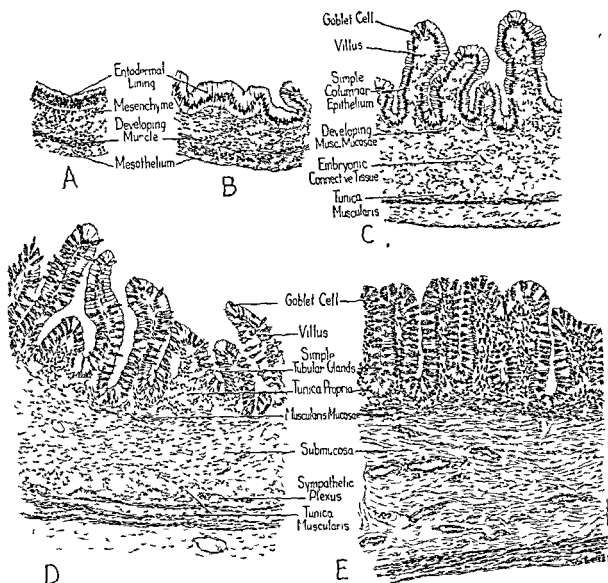


FIG. 281 Stages in histogenesis of large intestine. Projection drawings, $\times 100$, from human embryos in University of Michigan Collection. A, At 25 mm (eighth week). B, At 47 mm (tenth week). C, At 65 mm (eleventh week). D, At 104 mm (fourteenth week). E, At term.

as lye, may develop a stenosis (stricture) or even a complete atresia of the esophagus as a result of the contracture of the scar tissue. Stenosis or atresia of the uterine tubes may be a sequel to gonorrheal salpingitis. Such cases, however, belong to the realm of pathology and what is of interest to us in the present connection is a stenosis or an atresia that appears congenitally as a result of abnormal embryological development.

There is a peculiar growth phase in the early development of the intestines which many believe may be involved in the occurrence of congenital intestinal

mucus, and bile from the developing digestive tract itself, plus material which comes into the tract secondarily from the swallowing of amniotic fluid. The ingested material includes desquamated epidermal cells, lanugo hairs, and a certain amount of the sebaceous secretion (vernix caseosa) which covers the fetal skin. Until after birth the intestinal contents are sterile but as soon as feeding by mouth begins a bacterial flora is acquired. The

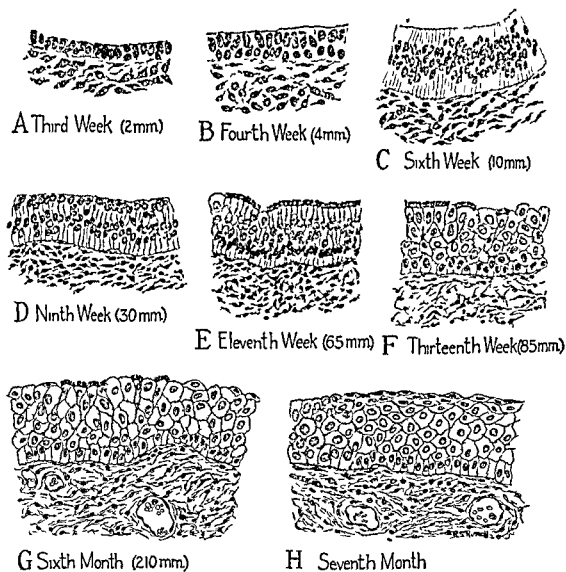


FIG. 280 Histogenesis of epithelial lining of esophagus. Projection drawings ($\times 300$) from University of Michigan series.

greenish color of the meconium, due to the long time it has been retained in the intestines subject to the action of bile, makes it readily distinguishable from the characteristic yellow color of the stools which begin following feeding. By the fourth day after birth all traces of meconial coloration should have disappeared from the intestinal contents, a fact which is sometimes of medicolegal value in establishing the time which has elapsed since birth.

Abnormalities of Digestive Tube Any abnormal narrowing of a tubular structure (such as a blood vessel or a duct or a part of the digestive tract)

superior mesenteric (omphalomesenteric) artery formerly followed along the yolk-stalk to break up in the vitelline plexus in the walls of the yolk-sac (Fig 398) Clinically a Meckel's diverticulum may behave as a second appendix Since it occurs in somewhere around 2 per cent of all individuals it must be considered among the possibilities in weighing the significance of atypical symptoms suggestive of appendicitis It is a curious fact that a Meckel's

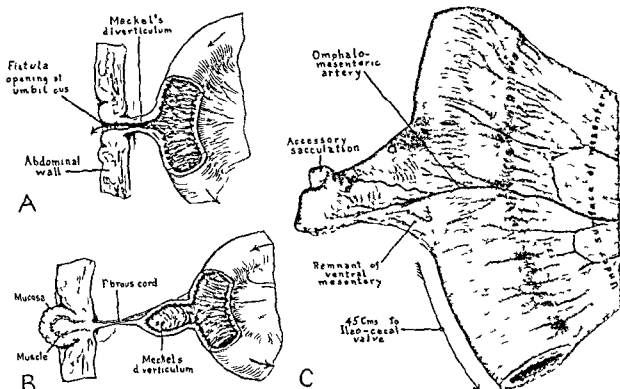


FIG 283 Three cases of Meckel's diverticulum (Redrawn from Cullen "Embryology, Anatomy and Diseases of the Umbilicus," courtesy, W B Saunders Co) A, Diverticulum with open connection at umbilicus B, Diverticulum connected to umbilicus by fibrous cord C, Detailed drawing of a Meckel's diverticulum ending as a blind pocket

diverticulum is quite likely to have patches in its mucosal lining with typical gastric-wall structure Such areas, when present, may be the site of peptic ulcers

GLANDS OF THE DIGESTIVE TRACT

In addition to the numberless small glands which are located in the walls of the digestive tract, there is a group of larger glands situated anatomically outside the walls of the tract but discharging into it by way of long ducts These extrinsically located glands are the major salivary glands, the pancreas, and the liver

Salivary Glands Except for the rostro-rodial portion of the hard palate and the gums, the entire oropharyngeal region of the adult is beset with small glands in its mucous lining Broadly speaking, these small glands are similar in origin and functional significance to the larger glands of this region and may be given the group designation minor salivary glands The major salivary glands are, of course, the parotids, submaxillaries, and sublinguals

atresia Toward the end of the second month, there is a tendency for the epithelial lining to begin to grow exuberantly before the size of the primitive gut tube has increased sufficiently to accommodate it. This is particularly likely to be marked in the esophagus and in the upper part of the small intestine, where, regularly at this age, the lumen will be found occluded by masses of epithelial cells (Fig 282, A, B). A similar condition occurs, also, in the rectum (Fig 282, C). In the normal course of events enlargement of the lumen of the gut follows closely after this stage, and the epithelial cells spread out and begin the orderly rearrangements by which the characteristic mucosal

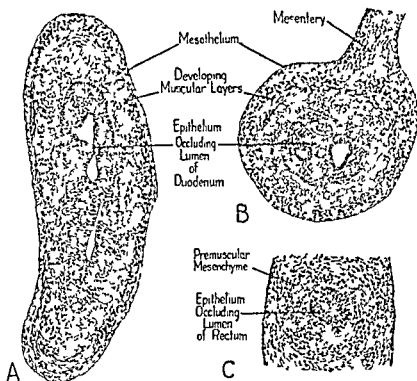


FIG 282 "Epithelial plug stage" in development of intestines. Projection drawings, $\times 100$, from sections of a human embryo of 17 mm. A, Small intestine, cut longitudinally. B, Small intestine, cut transversely. C, Rectum, cut transversely.

structure is attained. It is possible that failure to progress sufficiently promptly beyond this stage of transitory closure may be causally involved in the instances of congenital atresia of the intestines that occasionally present themselves as acute surgical cases.

One of the commonest of the anomalies of the intestines is known as *Meckel's diverticulum*. This is a sacculcation of the ileum which occurs about two to three feet above the ileocecal valve and represents a partial persistence of the yolk-stalk. It may be a blind pouch (Fig 283, C), or it may have retained an opening at the umbilicus. In the latter case it is said to be combined with an umbilical fecal fistula (Fig 283, A). The relations of one of the small terminal branches of the superior mesenteric artery to Meckel's diverticulum is highly characteristic and clearly suggests the way the main

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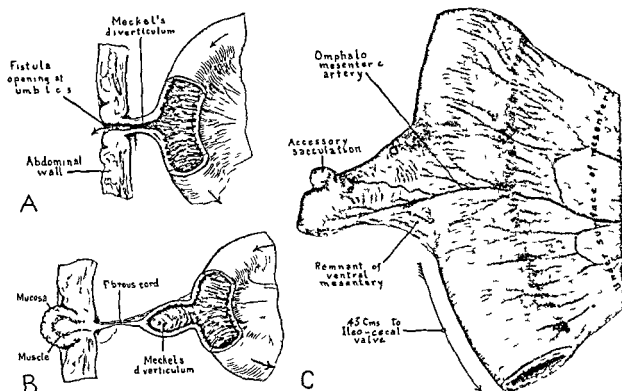


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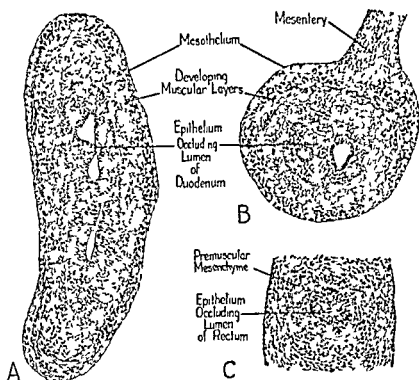


FIG 282 "Epithelial plug stage" in development of intestines. Projection drawings, $\times 100$, from sections of a human embryo of 17 mm. A, Small intestine, cut longitudinally. B, Small intestine, cut transversely. C, Rectum, cut transversely.

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into the underlying mesenchyme (Fig 284, B) It grows rapidly in length and turns back toward the ear When it has reached the territory near the ramus of the mandible, the main duct begins to branch freely into the primordial cell cords which will form the branch ducts and their terminal alveoli (Fig 285)

SUBMAXILLARY GLANDS The submaxillary glands ordinarily begin to show late in the sixth week as paired primordial cellular cords Each cord, representing the main duct of the gland on that side, arises near the mid-line under the tongue (Figs 285, 286, A) The duct grows back along the floor of the mouth and near the angle of the mandible turns ventrally (Fig 285) It then

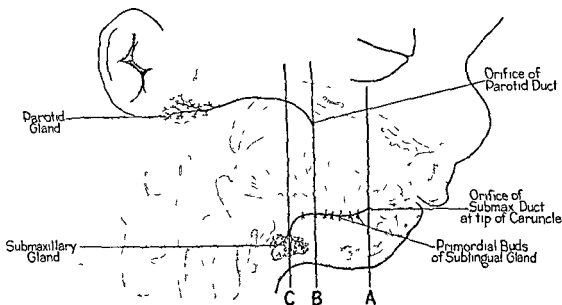


FIG 285 Schematic diagram showing developing salivary glands in a human embryo of the eleventh week Using a sagittal series of a 60-mm embryo (University of Michigan Coll, EH 23), the location of the glands and their ducts have been plotted within an outline of the head Certain landmarks in sagittal plane have been suggested by stippling Vertical lines indicate locations of frontal sections from another embryo of about same age shown in Fig 286

grows toward the surface pushing outside the border of the mylohyoid muscle before it begins to branch freely (Fig 286, C, D)

SUBLINGUAL GLANDS The sublingual glands arise slightly later than the submaxillaries Their primordia are usually recognizable by the end of the seventh week The sublingual glands are really a secondary grouping together of a row of small glands which arise independently Their secreting portions merge more or less within a common connective-tissue investment, but they retain their original ducts, each gland opening by a row of some 10 to 12 ducts emptying onto the floor of the mouth on either side of the roots of the tongue (Fig 285)

In the formation of any of the larger racemose glands, such as the salivary glands, the histogenetic processes are the same except for minor details The primordial cell mass destined to give rise to the epithelial (parenchymatous) part of the gland is formed by rapid proliferation of the cells in the deep

All of these glands arise in fundamentally the same manner, by the ingrowth of oral epithelium into the underlying mesenchyme. The major salivary glands are generally regarded as being derived from stomodaeal ectoderm, although the site of origin of the parotid is close to the zone where, when the oral plate ruptures, ectoderm and entoderm become continuous without any line of demarcation. Minor glands arise both on the ectodermal side and the entodermal side of this vague transition zone. The more rostrally located small glands such as those in the lips arise unquestionably from stomodaeal ectoderm. Many of the small glands, situated far back in the oropharynx, such

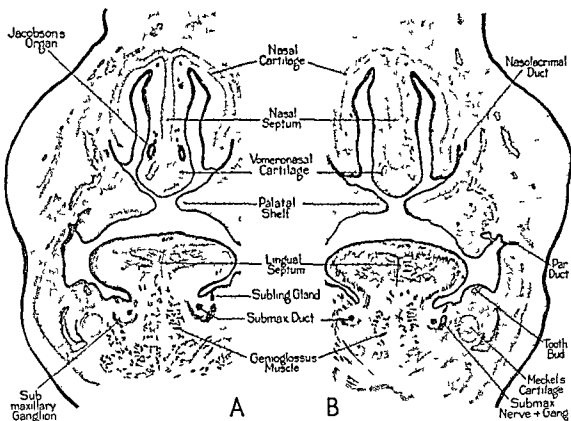


FIG. 284 Primordia of salivary glands in a human embryo of eighth week (University of Michigan Coll., EH 164, C-R, 25 mm) A, Section ($\times 20$) through primordia of one pair of the sublingual components B, Section ($\times 20$) through entrance of parotid duct into buccal cavity

as those around the base of the tongue and in the region of the tonsillar fossae, must be regarded as arising from pharyngeal entoderm. Interestingly enough, there are no histological differences in the adult glands of these different regions which give any suggestion of a difference in their origin. This is just another one among many facts suggesting the necessity of caution in regard to forming any too fixed ideas as to rigid limitations of the developmental potentialities of the primary germ layers.

PAROTID GLANDS The first of the salivary group to make their appearance are the parotid glands. Around the middle of the sixth week the start of an epithelial ingrowth can be made out on the inner surface of either cheek. This ingrowth is clearly recognizable in embryos of the eighth week extending

layer of the epithelium. The resulting cellular mass pushes into the underlying mesenchyme first as a solid epithelial cord. When the distal end of this primary cord has pushed out to the location where the secretory part of the gland is destined to be formed, it branches repeatedly. The terminal end of each branch carries a knoblike enlargement of somewhat radially arranged cells (Fig. 286, D). Hollowing out of this system of epithelial cords by cell rearrangement establishes the branching duct system of the gland. At the same time the terminal cell clusters become organized into the secreting units (acini). The connective-tissue framework (stroma) which supports the parenchyma of the gland is derived from the surrounding mesenchyme. As the small branch ducts and secretory acini develop from each of the main stems they form natural subgroupings of the growing glandular tissue. As the mesenchyme between such adjacent areas becomes developed into connective tissue, it tends to form septa which divide the gland into lobules. Meanwhile mesenchyme is concentrated about the expanding mass of the gland as a whole. As this peripheral zone of densely packed mesenchymal cells becomes specialized to form connective tissue, it forms a fibrous investment of the gland known as its capsule.

Such is the general outline of the events by which any of the racemose glands acquire their architecture. The specific characteristics of a particular gland depend on the cytological and physiological character of its secreting cells. For example, some of the acini of the salivary glands produce mucus which has merely a lubricating function while other acini produce a digestive enzyme, ptyalin, which is concerned in the conversion of starches to sugars. Recognition of such differences in the internal chemistry of cells depends on special cytological and microchemical techniques, discussion of which would carry us out of our present field and into that of the histologist.

Pancreas The pancreas is formed from two primordia which arise independently and later fuse with each other. These primordia are known as the dorsal and the ventral pancreatic buds, or, more briefly, as the dorsal and ventral pancreas. The dorsal pancreas arises, as its name implies, from the dorsal wall of the duodenum. It is located almost directly opposite the hepatic diverticulum which arises ventrally from the same part of the gut at about the same time (Fig. 70, D). In its growth the dorsal pancreas pushes between the two layers of splanchnic mesoderm which constitute the dorsal mesentery (Fig. 299 E).

The ventral pancreatic bud is an entodermal outgrowth which arises a little to the right of the mid-line and grows caudad, in the angle between the duodenum and the hepatic diverticulum (Fig. 287, A). As the hepatic diverticulum elongates it carries the ventral pancreatic bud with it so that the ventral pancreas soon appears to be a bud from the common bile duct (Fig. 287, B). In a certain number of cases two ventral pancreatic primordia appear, and it seems probable that the usual unilateral evagination seen in mammalian embryos represents what was originally a pair of ventrolateral diverticula. In the course of evolution one member of the pair appears to

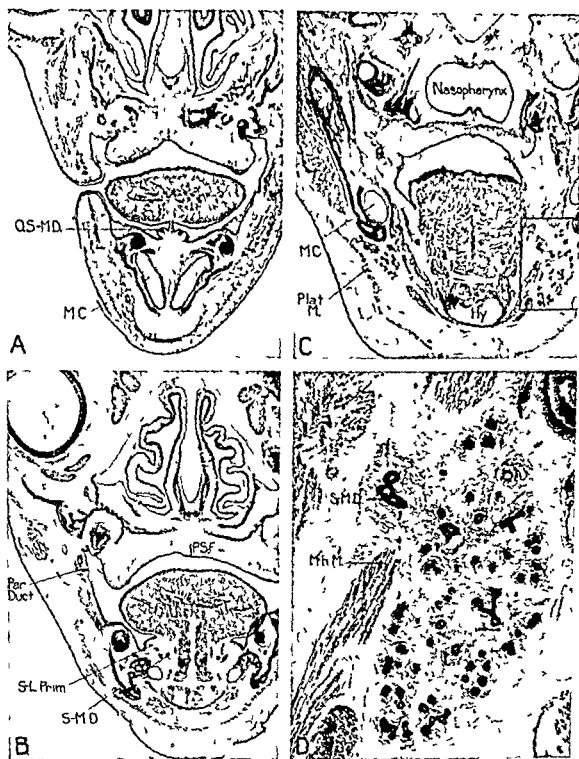


FIG 286 Developing salivary glands as seen in frontal sections of oro nasal region of a human embryo of about ten weeks (University of Michigan Coll, EH 198, C R, 55 mm) Locations of sections are indicated by the correspondingly lettered lines in Fig 285

Abbreviations Hy, hyoid cartilage, MC, Meckel's cartilage, Mh M, Myelohvond muscle, O S-M D, orifice of submaxillary duct at sublingual caruncle (papilla), Par D, parotid duct, Plat M, platysma muscle, P S F, epithelial remnant along line of fusion of palatal shelves, S-L Prim, epithelial bud constituting one of the series of primordia of the sublingual gland, S-M D, submaxillary duct

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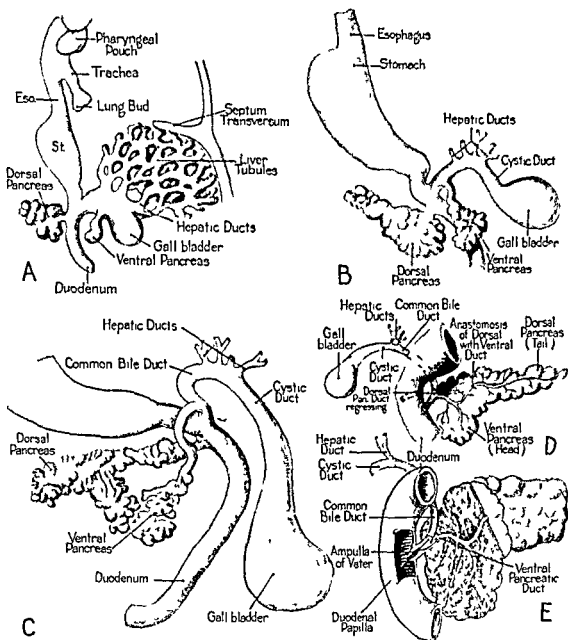


FIG. 287 Development of hepatic and pancreatic primordia A, Semi-schematic diagram based, in part, on Thyng's reconstructions of a 5.5-mm pig embryo. Stage of development is comparable to that in a human embryo early in fifth week B, Reconstruction from a 9.4-mm pig embryo. Stage of development is equivalent to that of a human embryo early in sixth week C, Schematized from Thyng's reconstruction of a 20-mm pig embryo—developmentally equivalent to a human embryo of seven weeks D, Schematic sketch showing dropping out of proximal part of dorsal pancreatic duct after its anastomosis with ventral duct E, Manner in which common bile duct and pancreatic duct become confluent in ampulla of Vater and discharge through duodenal papilla

have been suppressed, or possibly to have moved across the mid-line to become merged with its fellow

As the gut rotates and the common bile duct is bent to the right, the ventral pancreatic bud begins to grow around the right side of the duodenum (Fig 287, B) In its growth it pushes underneath the mesodermal covering of the duodenum and extends into the dorsal mesentery This brings it in juxtaposition with the dorsal pancreatic bud, with which it soon merges (Fig 287, C) The adult pancreas is chiefly derived from the dorsal pancreatic bud which gives rise to all the gland but the head Most of the head arises from the ventral bud In the coalescence of the primordial glandular tissue from these two independent sources the growing duct systems tend to fuse (Fig 287, D, E) The manner in which this takes place differs in different forms and is recorded in the arrangement of the adult pancreatic duct system In the horse and dog, for example, there are two ducts, a dorsal one (duct of Santorini) which opens directly into the duodenum, and a ventral one (duct of Wirsung) which opens into the duodenum by way of the common bile duct These two ducts represent the two original pancreatic buds which appear in mammalian embryos generally In other forms the two original ducts become confluent within the pancreas and the terminal portion of one duct only is retained Thus in man the ventral duct persists, communicating with the duodenum by way of the common bile duct, while the proximal portion of the dorsal duct usually atrophies The distal part of the original dorsal duct persists and drains the tail of the pancreas by way of its anastomosis with the ventral duct (Fig 287, D E) In the pig and the ox the ventral duct ordinarily disappears and the dorsal one persists as the definitive pancreatic duct

The development of the glandular tissue of the pancreas involves the same sort of budding and branching of primordial epithelial cell cords as that already described in connection with the development of the salivary glands Most of the enlarged terminal and lateral buds of the cell cords gradually take on the characteristic configuration of pancreatic acini while the cords themselves become hollowed out and form the ducts draining the acini (Fig 288)

The pancreas is peculiar in having scattered through its substance somewhere in the neighborhood of a million small clusters of secretory cells not discharging into the duct system but producing a hormone which passes directly into the blood stream These endocrine areas are the pancreatic islets (of Langerhans) The hormone (insulin) which they secrete is concerned in sugar metabolism The islands of Langerhans are of particular interest medically because disturbance of their endocrine function causes diabetes, a disease involving the breakdown of normal sugar metabolism with the resultant appearance of sugar in the urine The islets arise as specialized buds from the same epithelial cords which give rise to the typical secretory acini of the pancreas (Fig 288, E) The buds which are destined to form islets, however, tend to separate at an early stage from the parent tissue, and

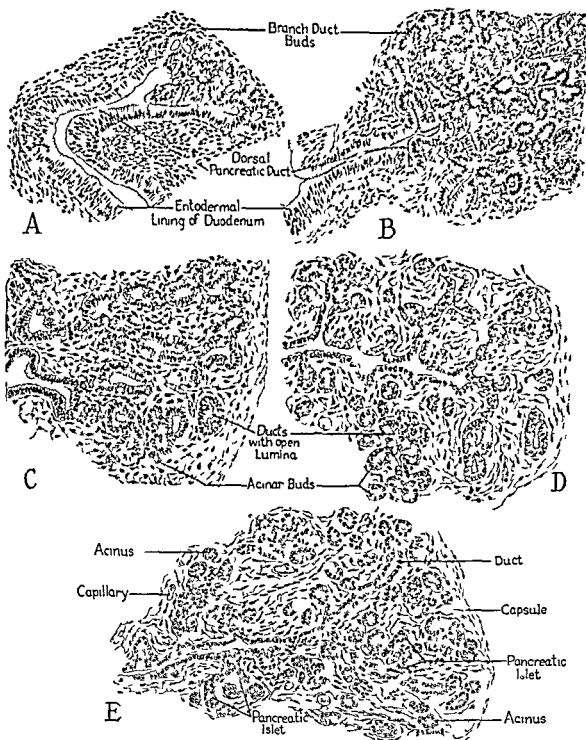


FIG 288 Stages in histogenesis of human pancreas Projection drawings ($\times 150$) from University of Michigan series A, Sixth week (EH 56, 10 mm) B Seventh week (LH 138, 17 mm) C, Eighth week (EH 164, 25 mm) D, 11 weeks (EH 173, I, 65 mm) E, 19 weeks (EH 143, H, 174 mm)

undergo independent differentiation into a peculiar, tangled knot of cellular cords with dilated capillaries in the interstices. Occasional islets retain their original connection with the duct system in the form of a slender strand of cells, but such connections, when they do persist, are merely vestigial and show no lumen.

Liver The primordial outgrowth of cells destined to form the secretory tubules of the liver, together with their duct system and the gall-bladder, is known as the hepatic diverticulum. It arises ventrally from the entodermal lining of the gut during the fourth week. When it first becomes recognizable it is little more than a thickened area of rapidly proliferating entodermal cells located on the lip of the anterior intestinal portal just caudal to the heart (Fig. 70, C). As closure of the foregut proceeds the hepatic primordium is incorporated into the floor of that part of the developing intestinal tract which becomes the duodenum (Fig. 70, D). This original diverticulum in embryos of 5 to 6 mm, has become clearly differentiated into several parts (Fig. 287, B). A maze of branching and anastomosing cell cords grows out from it ventrally and cephalically (Figs. 56, 287, A). The distal portions of these cords give rise to the secretory tubules of the liver, and their proximal portions form the hepatic ducts. As the young hepatic tubules grow, they push out between the two layers of splanchnic mesoderm which constitute the ventral mesentery at this level of the gut (Fig. 299, E). Their continued growth spreads the two mesodermal layers apart so they are reflected over the surface of the growing glandular mass of the liver. These investing mesodermal layers give rise to the fibrous connective-tissue capsule of the liver with its mesothelial covering, and to all the interstitial connective tissue of the liver lobules, as well as to the connective tissue and smooth muscle layers of its system of ducts.

Originating where the hepatic ducts become confluent is a local dilation of the original outgrowth which is the primordium of the gall-bladder. The early changes in the region of the gall-bladder and biliary ducts are shown in Figs. 287, C, D. The gall-bladder elongates very rapidly and its terminal portion becomes distinctly saccular. The narrow proximal portion of this limb of the diverticulum becomes the cystic duct. Numerous hepatic ducts open into the cystic duct. Toward the duodenum from the entrance of the hepatic ducts the original diverticulum is called the common bile duct (ductus choledochus).

The branching and anastomosing tubules which are distal continuations of the hepatic ducts constitute the actively secreting portion of the liver (Fig. 289). The hepatic tubules are not packed as closely together in a framework of dense connective tissue as is usually the case in massive glands. On the contrary, surprisingly little connective tissue is formed between them, and the intertubular spaces become pervaded by a maze of dilated and irregular capillaries known as sinusoids. This tremendously extensive meshwork of small blood vessels among the cords of liver cells is a condition which we

shall find of great importance in the development of the circulatory system in this region

The pattern of the branching of the growing hepatic tubules is quite characteristic and establishes the basic architectural plan of the adult liver. From each of the primary cell cords a series of branches grow out at right angles (Fig 290). Each of these branches in turn sprouts a system of radiating smaller branches (Fig 290). These radiating small branches become the tubules of a secretory lobule of the liver, and the axial cord of cells from which they arose serves as a branch of the hepatic duct system which drains such a lobule into one of the main ducts leading toward the gall-bladder.

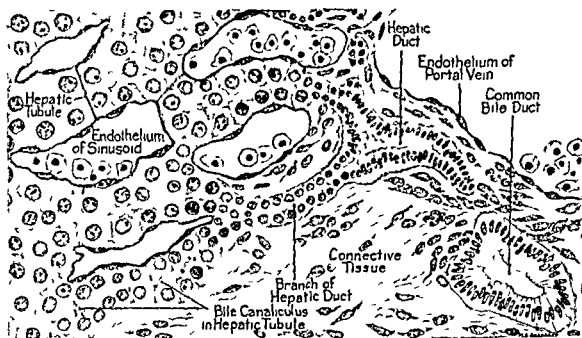


FIG. 289. Relations of hepatic ducts, tubules, and sinusoids in liver of a human embryo of six weeks (University of Michigan Coll., EH 262, 11.5 mm C-R).

The basic pattern of the glandular lobules of the liver becomes interrelated with an equally characteristic vascular pattern. As we have seen, the omphalomesenteric veins of young embryos return from the yolk-sac to the heart by way of the region in which the liver is developing (Fig 74). The growing cords of liver cells break up these veins into plexiform small vessels (sinusoids) which ramify in the spaces between the developing hepatic tubules (Figs 392, B-D). This is the first step toward establishing the characteristic hepatic portal circulation of the adult. After the yolk-sac undergoes regression the paired omphalomesenteric veins as they approach the liver become cross-connected and parts of each fall into disuse (Fig 406, B-D) thus giving rise to the unpaired portal vein characteristic of the adult (Fig 407). The distal tributaries now collect blood from the capillaries of the developing gastrointestinal tract and route it by way of the portal vein to the liver. The peculiarity of this arrangement is that blood which has already been through a

capillary bed in the intestines is carried, by a vein, to pass through a second set of capillaries in another organ instead of being returned directly to the heart. With reference to the liver this vein is advehent, a situation recognized in calling it the portal (carrying to) vein. After the blood has passed through the sinusoids of the liver it travels on toward the heart by way of the hepatic

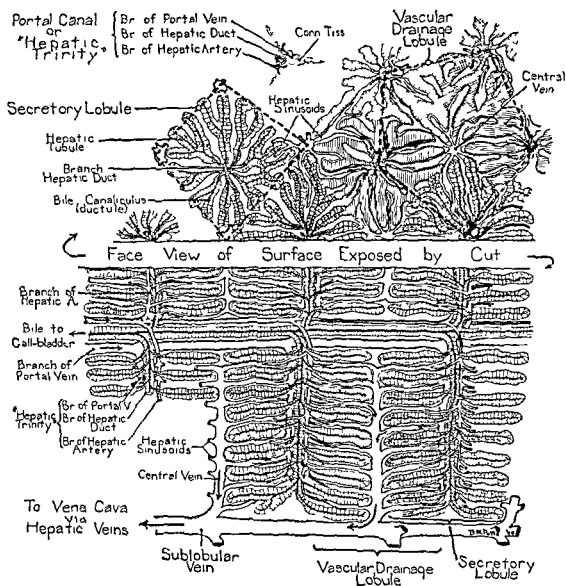


FIG. 290 Schematic diagram showing interrelations of secretory lobules and vascular drainage lobules in liver. Note especially that a vascular drainage lobule contains parts of a group of adjacent glandular lobules (See differential shading in lobule marked off by heavy broken lines, upper right). Observe, also, that the hepatic sinusoids serve as a common drainage channel for blood entering by hepatic artery and blood coming in by way of portal vein.

veins. These veins, which are efferent with reference to the liver, are derived from the omphalomesenteric veins proximal to the point where they were broken up by the growth of the liver (Fig. 406).

Naturally there must be mutual adaptation between such characteristic growth patterns as that of the hepatic glandular tissue and venous channels where they are developing simultaneously in a confined space. The basic

shall find of great importance in the development of the circulatory system in this region

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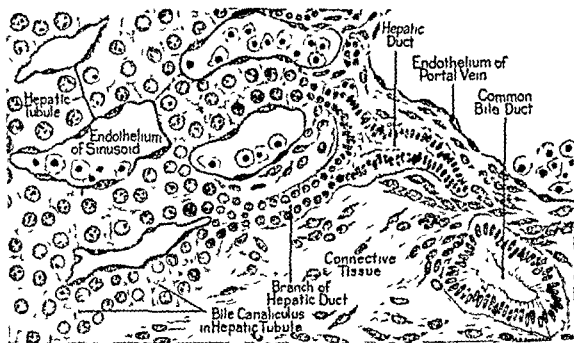


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RESPIRATORY SYSTEM

The upper part of the respiratory system has already been dealt with in other connections. The early development of the nasal region was considered with the development of the face. The manner in which the palate took shape and formed the floor of the nasal chambers was discussed in connection with the development of the oral region. Some of the later stages in the development of the nasal chambers, especially the differentiation of the olfactory regions, were taken up in the chapter on the sense organs. We may, therefore, begin the present section with a consideration of the laryngeal region.

Larynx The foundations for the formation of the larynx are laid very early, for it develops about the point of evagination of the primary respiratory primordium from the caudal part of the pharynx. Its lower portion is little more than trachea, somewhat enlarged and reinforced by heavier cartilages. Above the vocal cords it is essentially an entrance mechanism to the respiratory passages, so constructed and so operating under reflex control that it closes the air passages as food is swallowed. This upper part of the larynx centering around the epiglottis is derived from the floor of the pharynx adjacent to the glottis. In embryos of the fifth week vague swellings flanking the entrance to the primordial laryngotracheal outgrowth indicate the region where the arytenoid cartilages will form (Fig. 251, A, B). By the beginning of the sixth week a rounded mid-ventral prominence appears at the base of the third and fourth arches. As its position immediately cephalic to the glottis suggests, this elevation is the primordium of the epiglottis (Fig. 251, C). Coincidentally the arytenoid swellings begin to grow toward the base of the tongue. In so doing they soon begin to crowd against the epiglottis, adding a transverse component at the top of the sagittal slit which was the initial opening into the larynx and making it T-shaped (Cf Figs 251, B-D 291, A). It is at about this stage that exceedingly active growth of the laryngeal epithelium temporarily occludes the lumen in a manner similar to that we have seen occurring in the developing digestive tube. When the growth of the laryngeal walls becomes more rapid and the lumen is re-established the upper part of the entrance becomes more ovoid in shape although a deep inter-arytenoid notch still persists in the sagittal plane (Fig. 291, B). By the tenth week (Fig. 291, C) the major topographical features of the entrance to the larynx are already suggested. It is at about this time that the vocal cords begin to take shape on either side of the expanding laryngeal lumen. The later detailed molding takes place rather more slowly and it is not until the last third of gestation (Fig. 291, D) that the larynx takes on its definitive configuration.

Trachea The original laryngotracheal outgrowth, as we have seen in our study of young embryos, appears during the fourth week (Fig. 70, C, D). It is at first bluntly rounded and has an extensive communication with the ventrocaudal part of the pharynx. From this primordial outgrowth the trachea extends caudad, ventral to, and roughly parallel with the esophagus (Fig. 67). Almost from its first appearance the distal end of the outgrowth exhibits the

arrangement which results can best be characterized as an interdigitation of ducts and their tubules with hepatic veins and their tributaries (Fig 290). Since each system consists of radiating branches about a central stem, a striking overlapping of the radial systems occurs. Taking a hepatic duct as the center of a group of radially arranged secretory tubules, one has what could be called a secretory lobule (Fig 290). In the interstices between adjacent glandular units develop the veins that return the blood from the liver to the inferior vena cava. The venous drainage of a glandular lobule is consequently toward its periphery, and the blood is carried away from it by several different collecting veins (Fig 290). Conversely, if one examines the territory drained by any one of the many smaller veins that empty into the sublobular veins, one finds it composed of segments of the four to six adjacent secretory lobules (Fig 290). Since this drainage territory becomes more or less marked off by the spreading out of connective tissue from about the hepatic ducts, there develops a secondary, or venous drainage, lobule of the liver (Fig 290). It is this structural relationship that is recognized in designating the vein as the central vein of a liver (vascular) lobule.

Striking features of liver structure used as landmarks in both histology and pathology are the so-called portal canals. These are groups consisting of a hepatic duct, a branch of the portal vein, and a small arterial branch from the hepatic stem of the celiac artery, all supported close to one another by a common investment of connective tissue. This highly characteristic arrangement is a result of the way the afferent vessels of the liver in their growth tend to follow along with the epithelial system of ducts and tubules. A review of the diagrams in Fig 290 should make this relationship clear and serve, also, to emphasize that each portal canal is really the axis of a secretory lobule of the liver.

The double afferent blood supply to the liver is interesting from the functional standpoint. The small arterial branches seem to be distributed primarily to the stroma of the liver, but they must at the same time serve as the major source of the oxygen used by the liver as a whole. The portal circulation, postnatally, brings to the liver various types of food materials which have already been acted on in the gut tract (Fig 388). In the embryo no food materials are coming into the portal circulation from the gut tract, but the food-laden blood from the placenta enters the liver and joins the portal circulation (Fig 406). Thus in either the embryo or the adult the liver has first access to incoming food materials. In the embryo the combined portal and placental circulations far overshadow in volume the amount of blood coming into the liver by way of the hepatic artery. In the adult the disproportion is less but the portal circulation still brings in much the greater volume of blood. In neither embryo nor adult is there a separate venous return for the blood brought in by way of the hepatic artery. This blood after passing through small vessels in the stroma finds its way into the sinusoids that are fed by the portal veins (Fig 290) and thence into the central veins and back by way of the sublobular veins to the vena cava.

RESPIRATORY SYSTEM

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Almost from its first appearance the distal end of the outgrowth exhibits the

suggestion of a pair of knoblike enlargements which are called the lung buds, or somewhat more accurately, the primary bronchial buds (Fig 293, A, B). As the trachea elongates, the bronchial buds are carried progressively farther crudad in the body until they reach their definitive position in the thorax.

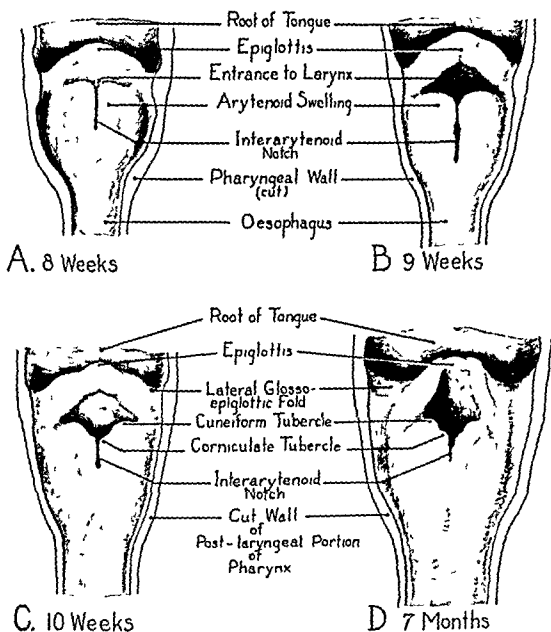


FIG 291 Four stages in development of larynx (Redrawn, with considerable modification, from Soulié and Bardier, *Jour de l'Anat et de la Phys*, Vol 42, 1907)

Only the epithelial lining and the glands of the trachea are derived from the original entodermal outgrowth from the pharynx. The cartilage, connective tissue, and muscle of its wall are formed by mesenchymal cells which become massed about the growing entodermal tube. During the eighth week it begins to be possible to distinguish between the part of the surrounding mesenchyme which is differentiating toward cartilage and that which is becoming muscle (Fig 292 A, B). By the end of the ninth week the developing cartilage

RESPIRATORY SYSTEM

are clearly delimited (Fig 292, C) Early in the fourth month the cord-primordia of the glands have begun to grow down from the lining epithelium into the underlying connective tissue (Fig 292, E) and in the next weeks these primordia rapidly differentiate into the characteristic configura-

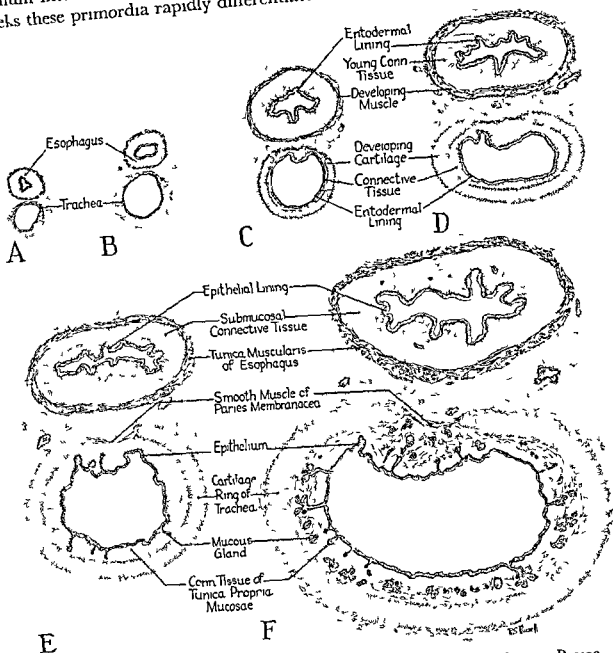


FIG 292 Development of layers in wall of trachea and esophagus. Projection drawings ($\times 20$) from series in University of Michigan Collection A, Early in seventh week (EH 102, 21½ mm) B, Middle of seventh week (EH 164, 25 mm) C, Nine weeks (EH 17, 39 mm) D, 11 weeks (EH 173, G, 65 mm) E, Fourteenth week (EH 145, G, 104 mm) F, Twentieth week (EH 34, X, 180 mm)

tion of the mucosal glands of the trachea. By the end of the fifth month all the major topographical features utilized in studying the histology of the adult trachea are clearly recognizable (Fig 292, F)

Bronchi and Lungs The right primary bronchus is from its first appearance somewhat larger than the left, and it tends to be directed less sharply to

the side. Although the difference in the angles of divergence of the two bronchi becomes less marked, it remains sufficient postnatally to account for the fact that foreign bodies enter the right bronchus more often than the left. During

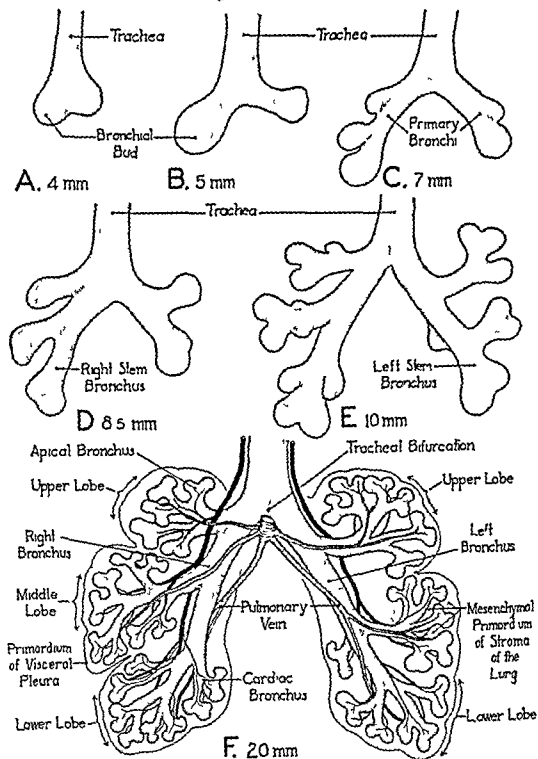


FIG. 293 Diagrams showing development of major bronchi of human lungs. Ventral views, adapted from various sources, chiefly Corning and Arey.

the fifth week the right primary bronchus gives rise to two lateral bronchial buds whereas only one is formed from the left. Each of these buds, and the bud at the distal end of each main or stem bronchus, is destined to branch and

rebranch to form the bronchial tree of a lobe of the adult lung. Thus, even at the beginning of the second month, there are forecast the three lobes characteristic of the right lung and the two that appear in the left (Fig 293 C, D).

The upper branch on the right is known as the apical, or eparterial bronchus. Its designation as eparterial is due to the fact that it lies upon (dorsal to) the pulmonary artery, whereas all the other main branches pass ventral to it (Fig 293, F). Later in development, as the heart and great vessels move caudad in the body, the eparterial bronchus crosses cephalic to the artery, but the equivocal word "upon" is still applicable in man if one thinks in terms of his erect posture. Although the term eparterial is a convenient one in descriptive anatomy, it seems doubtful that this relationship is of sufficient basic morphological importance to justify the emphasis which it customarily receives.

In the right lower lobe, also, there is a bronchial branch which does not have a symmetrical mate on the left. This is the so-called cardiac (infracardiac) bronchus. Its absence on the left is usually attributed to its being "crowded out" on that side by the growing heart. In this connection it seems pertinent to comment that one must be very cautious about accepting too literally such over-simple mechanical explanations of developmental processes. This is not meant to belittle the importance of mechanical factors in development, but to urge that they be kept in proper perspective. They appear so alluringly simple that they tempt one to overlook the more subtle, and often more important, factors of inherent developmental potentialities.

The early branching of the primary bronchi tends to be monopodial—that is to say, that a branch is formed on one side while the main stem continues to grow beyond the point of branching without essential change of direction (Fig 293, D, E). The branching after the main bronchi are established is more likely to be dichotomous, that is, there is bifurcation into two symmetrically placed branches neither of which extends in the original direction of growth (Fig 295, B, C). The bronchial tree of a pulmonary lobe is established by a continuation of this branching and rebranching process. By the sixth month approximately 17 orders of branches have been formed. From this time until birth increase in the complexity of the branching is very slight, and differentiation of the lobules already formed becomes the conspicuous feature of development. Even after birth, however, there is some additional branching continuing slowly through early childhood until the adult condition of about 24 orders of branches has been established.

The endodermal buds which constitute the primordium of the parenchymatous portion of the bronchi and lungs start to develop within a surrounding mass of mesenchyme flanked by splanchnic mesoderm (Fig 303, B). The arrangement of structures in this region, which will be known in adult anatomy as the dorsal part of the mediastinum, is suggestive of a broad mesentery supporting the lung buds ventral to the esophagus. As the lung buds grow they push out laterally into the parts of the coelom on either side of, and dorsal to, the heart. These regions of the coelom will eventually be

expanded and walled off to form the pleural cavities. In this process the splanchnic mesoderm is pushed out as a covering over the mesenchyme-packed bronchial trees (Figs 294, 295, 303, C, D). The splanchnic mesoderm becomes thinned to form the mesothelial layer of the pleura, and the immediately underlying mesenchyme becomes the connective-tissue layer of the pleura. The mesenchyme that serves as a loose, packing tissue about the developing endodermal tubes forms the stroma of the pulmonary lobules, and

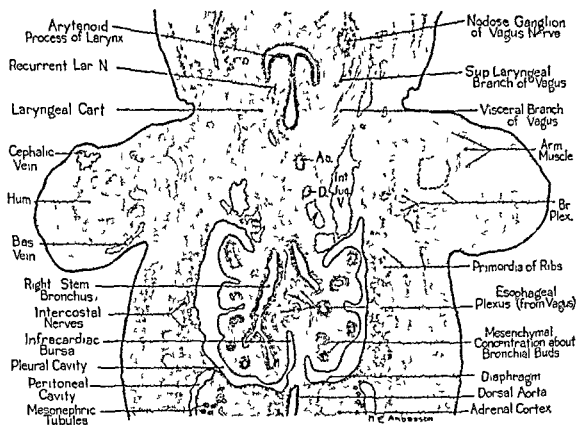


FIG 294 Frontal section of thoracic region of human embryo of 15 mm (seventh week) to show relation of developing lungs (Projection drawing, $\times 25$, from University of Michigan Coll., FH 227) D = ductus arteriosus

the cartilage plates, smooth muscle, and connective tissue which reinforce the epithelial lining of the bronchi.

After the bronchial tree has been established by successive branchings, the pulmonary lobules develop by expansion and elaboration of the myriads of terminal buds. The branching, which tended to be dichotomous while the bronchial system was being established, now becomes quite irregular (Cf Fig 295, C with 296, 297). Each terminal or respiratory bronchiole develops a series of sacculations extending out in all directions so that in a single section only part of the branches are seen and it is necessary to have recourse to casts, or to wax-plate reconstructions, to demonstrate the full complexity of the system. There is much variability in pattern but generally each terminal bronchus divides into from three to six irregular passages called alveolar ducts (Fig 297, A). Each alveolar duct at first ends in a bulging sac of cuboidal to columnar epithelium (Fig 296). During the sixth month these terminal por-

tions become irregularly out-pocketed to form the numerous alveolar sacs (alveoli) which open into the alveolar ducts (Fig 297, A) Almost as soon as they are established in their definitive relations, the alveoli begin to show radical changes in the character of their epithelial lining Starting in irregular patches the hitherto columnar epithelium thins to squamous (Fig 297, D)

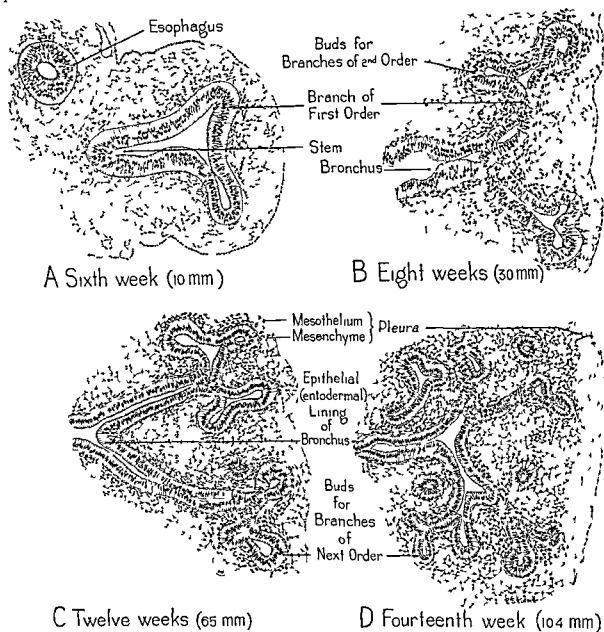


FIG 295 Projection drawings ($\times 100$) showing four early stages in histogenesis of lungs A, Embryo of sixth week (EH 56, C-R, 10 mm) B, Embryo of eight weeks (EH 15, C-R, 30 mm) C, Embryo of 11 weeks (EH 173, B, C-R, 65 mm) D, Embryo of fourteenth week (EH 145, C, C-R, 104 mm)

As the respiratory areas are extended with the formation of additional alveolar sacs, the thinning of the epithelium involves more and more of the walls. At the same time the capillaries of the pulmonary circuit increase the richness of their meshwork and capillary loops begin to bulge through the thinned epithelium so the blood in the capillaries is separated from the lumen of the alveolar sacs by the thinnest of films of cytoplasm (Fig 297, D). Many his-

tologists believe these capillary loops ultimately push completely through the thinned epithelium lining the alveoli so that only the vascular endothelium separates the blood from the air in the alveoli. This point is one of considerable theoretical interest, but more important than the controverted details as to the manner in which it is accomplished, is the basic fact that the epithelial lining becomes sufficiently thinned to permit ready exchanges of oxygen and

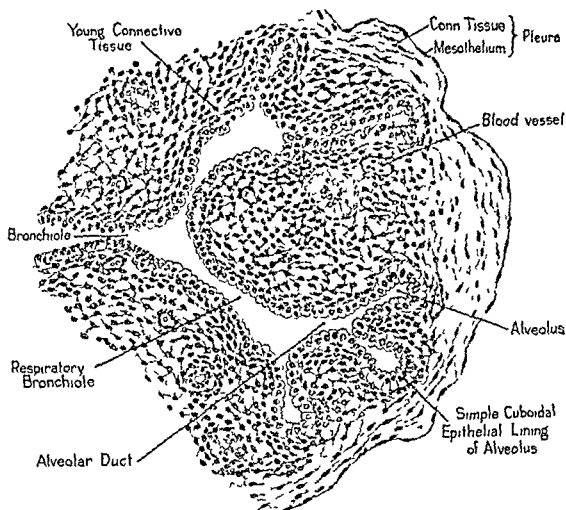


FIG. 296 Projection drawing ($\times 300$) of a pulmonary lobule from an embryo toward end of fifth month of development (University of Michigan Coll., EH 143, C-R, 174 mm.) Compare with Fig. 297, D, showing a corresponding area from a somewhat older embryo in which the thinning out of the epithelial lining of the alveoli has commenced.

carbon dioxide between the blood in the pulmonary capillaries and the air in the alveoli. When this has been accomplished one of the essential developmental prerequisites for postnatal survival has been met.

It is known that thoracic movements of a respiratory type may occur in older fetuses in utero. There is still difference of opinion as to whether this is a regular phenomenon, or whether it occurs only when for some reason the fetus does not receive an adequate supply of oxygen by way of the placental circulation. Certainly in experimental animals an artificially produced anoxemia of the fetus causes vigorous respiratory movements, but that does not

necessarily mean that such movements may not also occur spontaneously under other circumstances Much further work is needed on this recently opened and very interesting subject

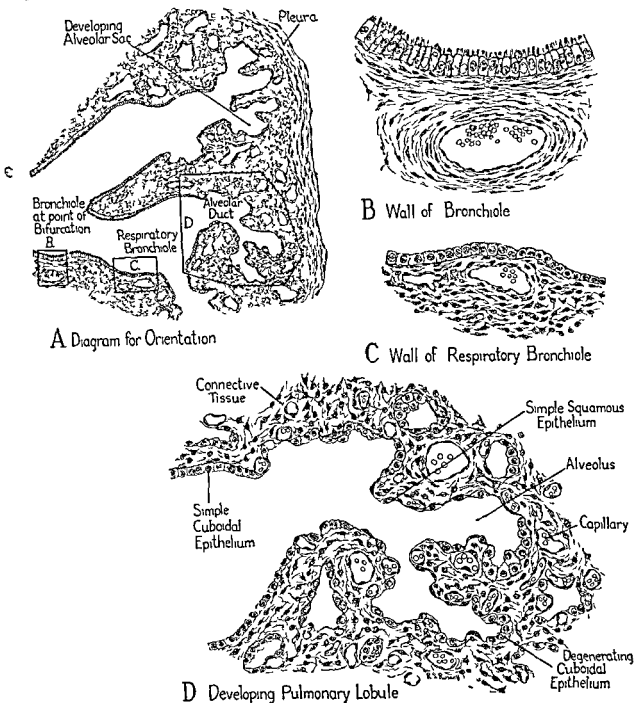


FIG 297 Development of the finer structure of the lungs as seen during the sixth month (Projection drawings from University of Michigan Coll, EH 221, C-R, 200 mm) A, Orienting diagram, $\times 100$, with locations of areas shown enlarged in B, C, and D indicated B, Wall of a bronchiole, $\times 300$ C, Wall of respiratory bronchiole, $\times 300$ D, Part of a pulmonary lobule, $\times 300$

The partial distension of the pulmonary lobules regularly seen in sections of certain areas of fetal lungs strongly suggests that the aspiration of a certain amount of amniotic fluid is a regular intra-uterine occurrence This seems reasonably well supported by experiments in which dyes or particulate matter

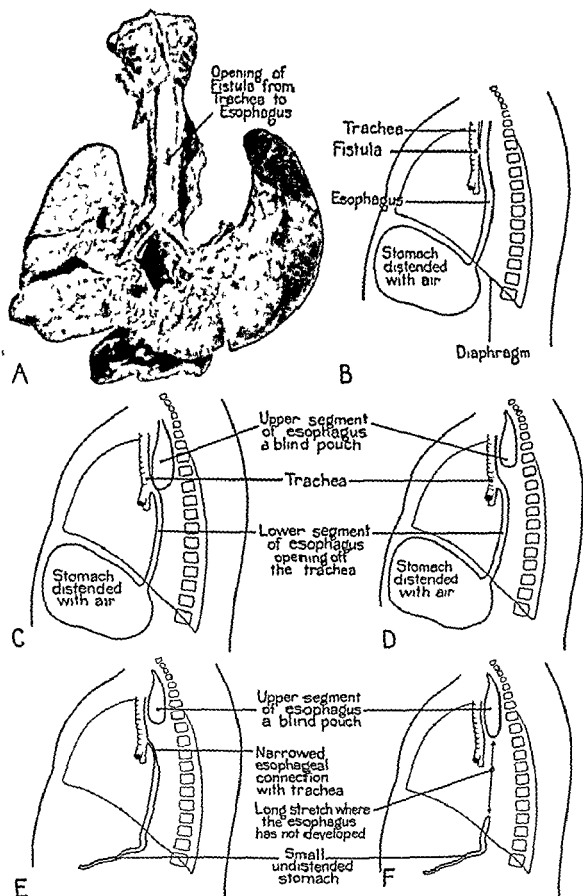


FIG. 298 (For legend see p. 497)

injected into the amniotic fluid of experimental animals have been recovered from the lungs. The fetal lung as a whole, however, has its air spaces undistended and on casual microscopic inspection looks more like a gland than like an adult lung. Moreover, it is sufficiently compact so that it will sink when placed in water. In contrast a lung which has been active in respiration will, even at autopsy, retain enough air to cause it to float. This fact may be of medicolegal significance in establishing whether an infant was stillborn or had lived for a time after birth. In this connection it should be realized that the entire lung does not become fully inflated as soon as respiration starts. For the first week to ten days after birth there are likely to remain parts of the lungs which are uninflated (atelectatic), although after the first day or two such areas are relatively small.

Abnormalities of Respiratory System Serious abnormalities of the larynx are very rare. Most of its departures from the normal are in matters of size or proportions. The whole organ may be large or small, and the shape of the laryngeal ventricles is subject to great variation.

The commonest anomaly of the trachea of serious clinical significance is a condition in which there is an abnormal opening between the trachea and the esophagus below the level of the larynx. This condition is known technically as a tracheo-esophageal fistula (Fig 298). Such a fistula may be merely a small opening between an otherwise fairly normal trachea and esophagus, or it may be a large opening co-existing with an atresia of the esophagus. In such a case the esophagus usually ends as a blind pouch not far from the level of the fistula. A newborn infant with such a developmental defect may appear normal and start to breathe without difficulty. With the first attempts at nursing, however, there will be backing up of milk from the blind esophagus into the trachea with a resulting infection (aspiration pneumonia) of the lungs. Only recently have such cases been successfully dealt with surgically. The

FIG 298 Figures illustrating conditions encountered in a series of cases of tracheo-esophageal fistula. (After Cameron Haight.) A, Photograph of dissected specimen to show location of opening in an uncomplicated case of tracheo-esophageal fistula (Autopsy specimen from University of Michigan Hospital, Case 541745). B, Lateral view diagram to show relations of trachea and esophagus in case illustrated in A. C-F, Diagrams illustrating conditions encountered in a series of cases of tracheo-esophageal fistula accompanied by varying degrees of agenesis of the esophagus. (From Haight, *Annals of Surgery*, Vol 120, 1944.) In the type of case represented by C there was interruption of the esophageal lumen but some continuity of its muscular walls. In the type of case schematized by D there was complete interruption of the esophagus, the upper segment ending as a blind pouch and the lower segment having a lumen continuous with that of the trachea. Note the way in which the stomach was distended with air entering by way of the trachea. Cases of the type diagrammed in E showed fundamentally the same relations as the D group as far as the upper segment of the esophagus was concerned, but exhibited varying degrees of narrowing of the esophageal connection with the trachea. In the group represented by F there was a considerable section of the esophagus that had failed to develop and neither the upper nor the lower segment communicated with the trachea. In his series of 35 cases in which the conditions were accurately determined at operation, Dr Haight (personal communication) has encountered one case of type A, nine cases of type C, 20 cases of type D, four cases of type E, and two of type F.

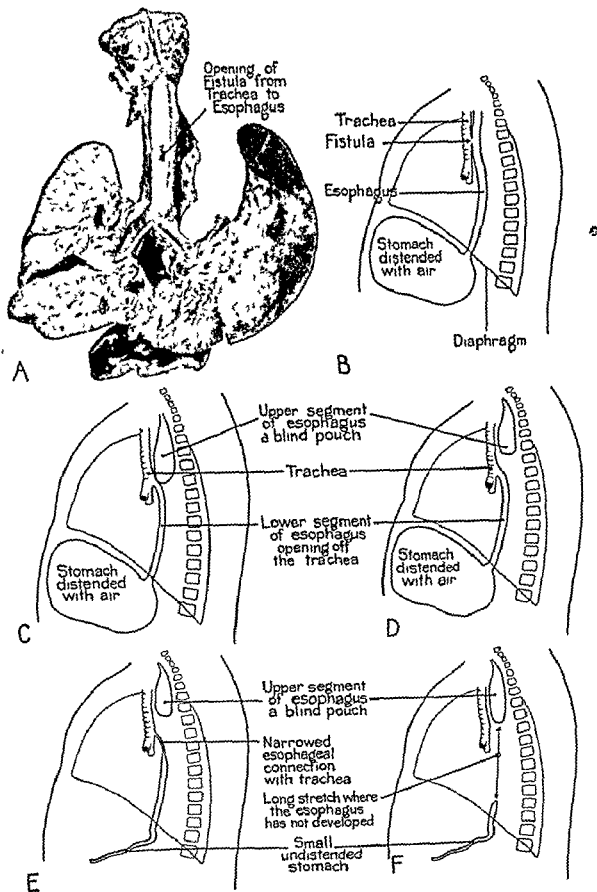


FIG. 298 (For legend see p. 497)

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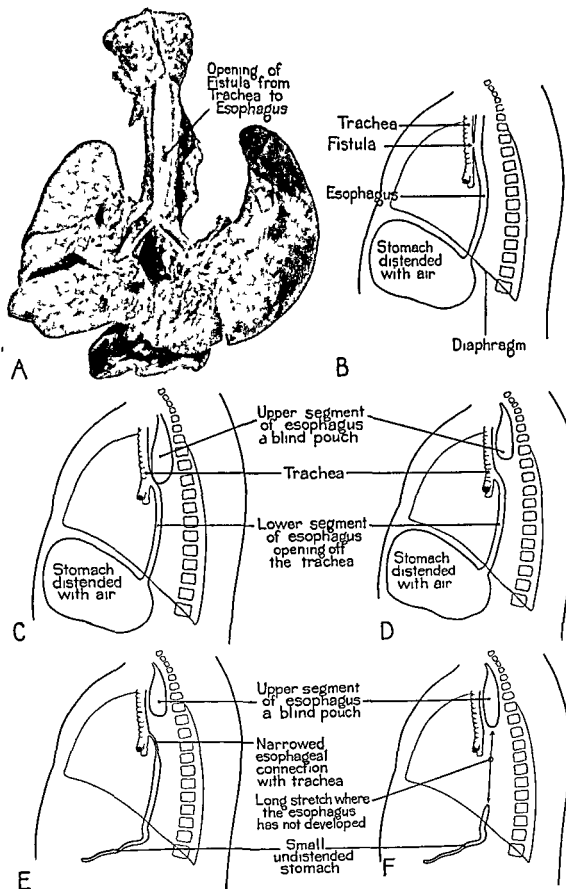


FIG 298 (For legend see p 497)

Body Cavities and Mesenteries

BODY CAVITIES

The body cavities of adult mammals are (1) the pericardial cavity containing the heart, (2) the paired pleural cavities containing the lungs, and (3) the peritoneal cavity containing the viscera lying caudal to the diaphragm. All three of these regional divisions of the body cavity are derived from the coelom of the embryo. The originally continuous coelom is separated into these definitive subdivisions by three partitions: (1) The unpaired septum transversum which serves as a sort of incomplete, provisional diaphragm, (2) paired pleuropericardial folds which are attached to the septum transversum and complete the division between the pericardial and pleural cavities, and (3) paired pleuroperitoneal folds which are also continuous with the septum transversum and complete the partition between the pleural cavity on either side and the peritoneal cavity. The general location and relations of the coelom are already familiar from the study of young embryos, but it may be well, nevertheless, to review some of the more important of the early relations before considering the manner in which the adult divisions are established.

Primitive Coelom The coelom arises by the splitting of the lateral mesoderm on either side of the body into splanchnic and somatic layers (Fig 299). It is, therefore, primarily a pair of cavities each of which is bounded mesially by splanchnic mesoderm and distally by somatic mesoderm. In forms such as birds and mammals which have highly developed extra-embryonic membranes, the coelom extends between the mesodermal layers of the extra-embryonic membranes, far beyond the confines of the developing body. In mammals the nutrition of the embryo depends on the uterine relations established by the extra-embryonic membranes and they develop exceedingly precociously. It is not surprising, in view of this fact, that the splitting of the mesoderm in mammals occurs first extra-embryonically and progresses thence toward the embryo (Fig 299, A, B). When the body of the embryo is folded off from the extra-embryonic membranes, the extra- and intra-embryonic portions of the coelom are thereby separated from each other, the last place of confluence to be closed off being in the region of the belly-stalk (Fig 299, C). It is the intra-embryonic portion of the primitive coelom, thus delimited, which gives rise to the body cavities.

It will be recalled that the typical configuration of the mesoderm as

operation must be immediate and radical, and the mediastinum is one of the most difficult parts of the body in which to operate. In many cases the agenesis of the esophagus is such that establishing its continuity is not possible. In spite of the hazards and the inevitable failures, the cases which are successfully operated upon are technical triumphs and such operations offer the only chance of survival to individuals with this defect.

As one might expect, the complicated pattern of branching of the bronchial tubes is likely to show considerable departures from the usual plan. Such variations even when they affect the larger bronchi are ordinarily of little functional significance to the individual. They are likely to be of interest clinically only in case some such accident as the lodgment of a foreign body necessitates the use of a bronchoscope. Much more significant medically is a malformation of the terminal parts of bronchial trees known as bronchiectasis. When this condition is of developmental origin some of the terminal bronchi form irregular saccular enlargements that are not molded into normal pulmonary lobules. These sacs drain poorly and are subject to chronic infection which may in time cause serious or even fatal damage to the lungs.

The lungs may be secondarily involved by abnormal conditions which arise primarily elsewhere. For example, in situs inversus of the viscera (Fig. 317) the apex of the heart points to the right instead of the left, and in such cases it will be the right lung that exhibits only two lobes while the left lung will be three-lobed. Again in a case of diaphragmatic hernia the pleural sac is invaded by parts of the gastro-intestinal tract (Fig. 306). It is such a condition that one occasionally sees ineptly publicized in the daily papers as a case of "upside-down stomach." In such individuals the lung on the affected side has its efficiency seriously reduced. In most such cases the heart also has its action handicapped because of compression of the pericardial space. Fortunately, return of the abdominal viscera to their proper location and repair of the gap in the diaphragm is usually successful when undertaken by a competent surgeon.

Primary Relations in Pericardial Part of the Coelom In connection with the formation of the heart we have already become familiar with some of the primary relations in that part of the coelom which is destined to be walled off as the pericardial cavity of the adult. It will be recalled that this is the first intra-embryonic part of the coelom to be established by splitting of the mesoderm into splanchnic and somatic layers (Figs 38, I, 72, A). As is the case with the coelom as a whole, the pericardial region is at first represented by paired right and left cavities. In its differentiation, as well as in its initial appearance, the pericardial part of the coelom is precocious, for it is the first region in which the primitive paired coelomic chambers become

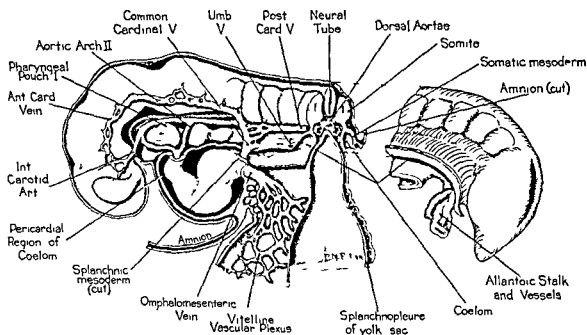


FIG 300 Schematized lateral dissection of human embryo of about three weeks to show continuity of pericardial portion of coelom with paired coelomic chambers of mid-body region (Based, in part, on Heuser's study of a 14-somite embryo, Carnegie Coll., 4529 Cf Fig 50, B)

confluent to establish an unpaired condition such as exists in the adult (Fig 72, B-D). During the time it is thus being established, the pericardial cavity is in open communication caudally, on either side, with the still paired coelomic chambers of the mid-body region (Fig 300).

Septum Transversum The first indication of the partitioning off of the pericardial region from the rest of the coelom is given by the formation of the septum transversum. This aptly named structure consists at first of a loosely organized, transversely placed mass of mesoderm situated just caudal to the heart and extending dorsad from the ventral body-wall. At this stage it is essentially a shelf-like structure between the heart and the liver. Its cardiac face is clothed with a smooth mesothelial lining, but the liver grows into its caudal face so there is on that side merely a transition to glandular tissue rather than a definite boundary (Fig 56). As the liver becomes more highly differentiated its border becomes more clear-cut and the boundary between liver and septum transversum becomes correspondingly more sharply defined.

indicated diagrammatically in Fig 299 does not pertain in the cephalic part of the embryo. The mesoderm in the head region consists of mesenchymal cells which wander in from the more definitely organized mesoderm located

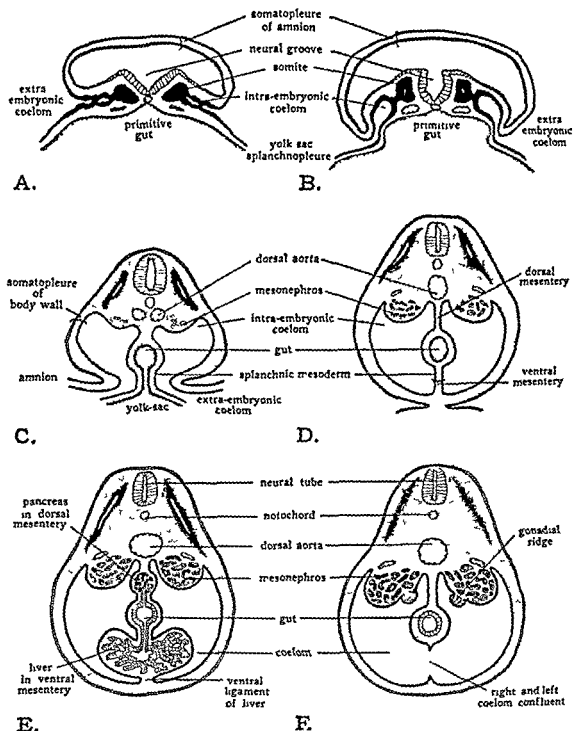


FIG 299 Diagrams illustrating early stages in development of coelom and mesenteries

farther caudally in the body. Thus the intra-embryonic coelom established by the splitting of the lateral mesoderm extends cephalad only to the level of the pharynx, and the heart is developed in its most anterior portion (Fig 300)

bulge out laterally into them (Fig 301) Later, as we shall see, these narrow pleural cavities become greatly enlarged to accommodate the growing lungs (Fig 303)

Pleuropericardial and Pleuroperitoneal Folds The complete isolation from one another of the pericardial, pleural, and peritoneal portions of the coelom is brought about by the growth of additional folds which become

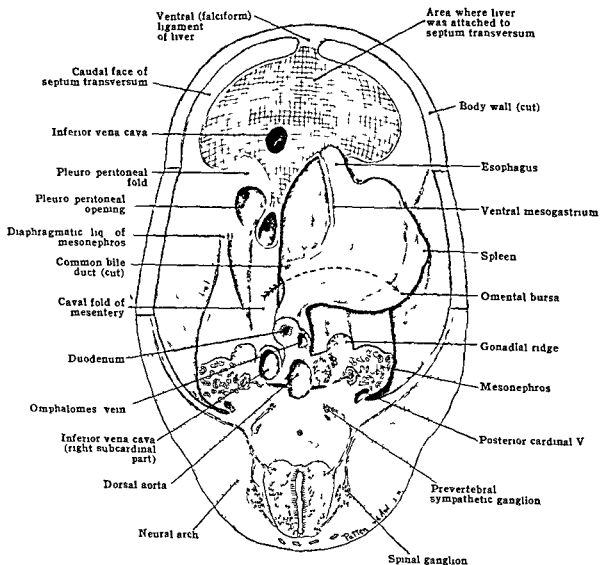


FIG 302 Dissection to show right pleuroperitoneal opening in developing diaphragm exposed by removal of liver Preparation is viewed from below, looking cephalad

associated with the septum transversum These folds arise on either side, from the dorsolateral body-walls where the ducts of Cuvier, as they swing around to enter the sinus venosus of the heart, cause the body-walls to bulge into the pleural canal (Fig 303, B) On either side, the fold extending cephalad from this primary elevation about the duct of Cuvier is called the pleuropericardial fold, and the fold which extends caudad is called the pleuroperitoneal fold (Figs 301, B, 308)

The pleuropericardial folds arising on the cephalic border of the primary ridges grow cephalad and mesiad The caudal borders of these roughly tri-

The septum transversum must not be thought of as the primordium of the entire diaphragm. The diaphragm is a composite structure of which the septum transversum forms only the more ventral portions (Fig 305, A). It never, itself, extends all the way to the dorsal body-wall. Nevertheless, the division of the coelom into thoracic and abdominal regions is already at this early stage clearly foreshadowed by the position of the septum transversum.

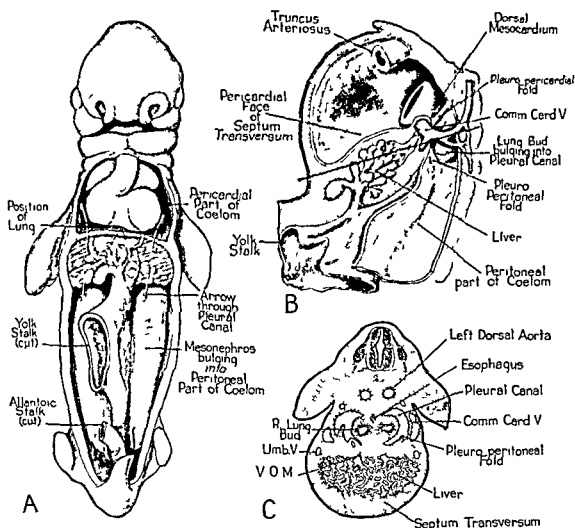


FIG 301 Relations of various parts of coelom during fifth week. A, Semi-schematic frontal plan. Arrows indicate location of pleural canals, on either side, dorsal to liver. B, Lateral dissection to show left pleural canal opened with lung bud bulging into it medially (Modified from Kollmann). C, Section through body of an 8 mm embryo, schematized to show relations at level of pleural canal. Level of section is indicated by heavy line across B.

Pleural Canals. Dorsal to the septum transversum, the region of the coelom occupied by the heart is confluent with that occupied by the stomach, liver, and intestines. At this level the mass of the liver, in conjunction with that of the septum transversum, acts as a barrier to the ventral extension of the primary right and left coelomic chambers and they remain for a time relatively unexpanded as the so-called pleural canals. These canals lie either side of the mediastinal region, and when the trachea bifurcates the lung buds

at the same time brings the pleuroperitoneal membranes into such a position that they appear to continue the septum transversum toward the dorsal body-wall. For a time yet there is an opening from each enlarging pleural chamber into the peritoneal part of the coelom (Figs 302, 308). This, however, becomes progressively smaller and ordinarily closes in embryos of about 19 to 21 mm (beginning of eighth week).

Diaphragm With the closure of the pleuroperitoneal opening, the septum transversum and the pleuroperitoneal folds have combined to separate the thoracic cavities from the abdominal part of the coelom and we may say that the diaphragm has been established. A diaphragm which completely separates the pleural cavities from the abdominal cavity is characteristic of the mammals. Such a complete separation permits the establishing of negative pressure in the pleural chambers, thereby increasing the efficiency of the mechanism of inspiration.

During the course of development the septum transversum moves an astonishing distance caudad in the body. In an embryo of about three weeks the heart lies—so to speak—under the chin, that is at this stage opposite the occipital and the uppermost of the cervical myotomes (Fig 304, A). The chief nerve to the diaphragm is the phrenic, which begins to send fibers to the premuscular masses of mesenchyme when they lie at the level of the third, fourth, and fifth cervical nerves (Figs 304, B, 189). In embryos of the sixth week the developing diaphragm has moved caudad beyond the point of origin of its nerve fibers so that the phrenic nerve begins to take on a descending course (Figs 304, C, D, 199, 190). As the diaphragm moves relatively farther caudad in the body, the phrenic nerve is correspondingly lengthened. In embryos of the eighth week the lungs have pushed the dorsal parts of the diaphragm far caudad, giving the diaphragm as a whole a strongly domed contour. This brings the attachment of the diaphragm to the dorsal body-wall down to the level of the lowest thoracic or the first lumbar segment (Fig 304, E, G), practically its adult level.

Relatively late in its development the diaphragm receives a secondary ingrowth of muscles from the body-walls. Thus the completed diaphragm is derived developmentally from four sources: (1) An unpaired ventral portion from the septum transversum, (2) paired dorsolateral portions from the pleuroperitoneal membranes, (3) an irregular median dorsal portion from persisting parts of the primary mesentery caught between, and fused with, the septum transversum and the pleuroperitoneal portions, and (4) marginal ingrowths of body-wall muscle (Fig 305, A).

Later Changes in Relations of Pleural and Pericardial Chambers We have already seen how the lungs, starting to develop dorsally in the small pleural canals, push ventrally to form enlarged pleural chambers (Fig 303, C, D). In this process space is made for the lungs at the expense of the loose mesenchymal tissue of the young body-walls. As they advance, the lungs separate off a sheet of body-wall tissue which is in effect added to the pleuropericardial membranes. Thus the lungs and the pleuropericardial membranes

angular folds are from the first continuous with the dorsal margin of the septum transversum. When their cephalic borders meet and fuse with each other and with the mediastinum they complete the separation of the pericardial cavity from the rest of the coelom (Fig 303, C).

The pleuroperitoneal folds arise along the caudal borders of the primary ridges overlying the common cardinal veins (Fig 301, B, C). These folds are, also, more or less triangular in shape, and for descriptive purposes we can

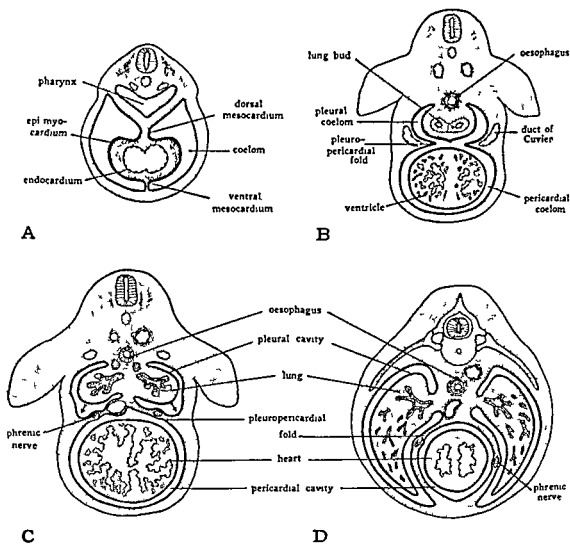


FIG 303 Schematic diagrams showing manner in which pleural and pericardial regions of coelom become separated

regard the base of the triangle as being along the body-wall, and the apex as being attached to the septum transversum. The cephalic margin would then be along the line of origin from the cardinal ridge while the caudal margin projects into the pleural canal (Fig 301, B, C, 308). As the lungs grow, we have seen that they push ventrad, excavating increasingly capacious spaces for themselves (Cf Fig 303 C, D). At the same time they extend also caudad, making the original pleuroperitoneal membranes more extensive by dissecting them away—speaking figuratively—from the dorsolateral body-walls. This

gradually come to lie on either side of the heart in their characteristic adult relations (Cf Figs 303, D, 305, C, 313) This same series of changes swings around the lines of attachment of the pleuropericardial folds on the cephalic face of the diaphragm so that the pleuropericardial membranes come to be attached in practically a dorsoventral direction With these changes in mind

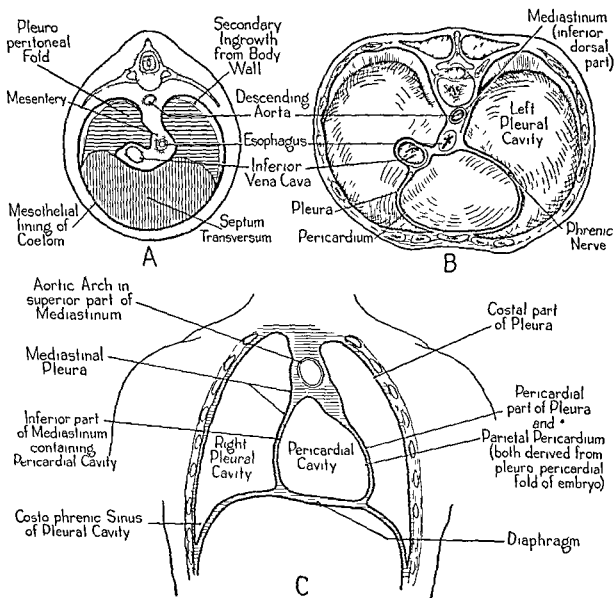


FIG 305 Diaphragm in embryo and in adult A, Diagram indicating embryological origin of various regions of diaphragm (Modified from Broman) B, Thoracic face of adult diaphragm (Modified from Rauber-Kopsch) C, Relations of diaphragm as seen in a frontal section of adult body (Modified from Rauber-Kopsch)

we can at once recognize that it is the original cardiac face of the pleuropericardial fold which now constitutes the lateral parts of the pericardium What in adult anatomy is called the mediastinal portion of the parietal pleura is, of course, merely the lungward face of the original pleuropericardial fold flaunting a new name (Cf Figs 303, 305, 313) Arising as these layers do as the opposite faces of the same fold, it seems only natural that in the adult we find them intimately fused back to back

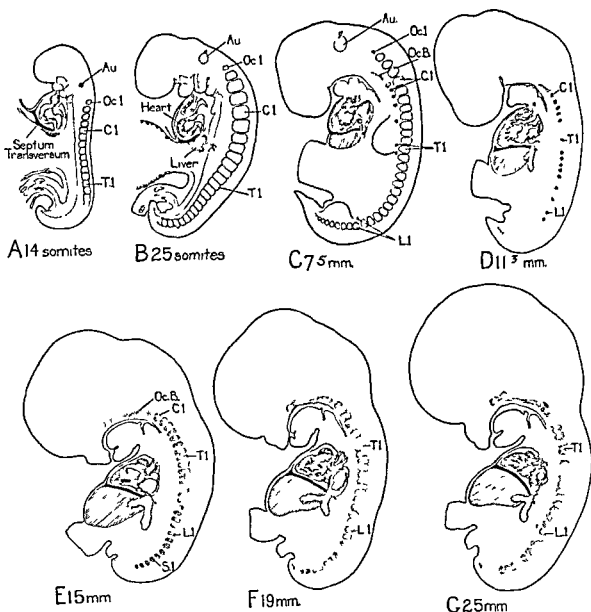


FIG 304 Diagrams to show changes in position of septum transversum between third and eighth week of embryonic life. Septum transversum is drawn in solid black. Broken line extending dorsocaudally in D-G indicates contour of pleuroperitoneal portion of diaphragm as seen in sections on either side of mid line. In the two youngest stages no vertebral primordia have been formed, therefore somites are used to indicate metameric level at which septum transversum lies. By beginning of sixth week vertebral levels are indicated by sclerotomal concentrations which are drawn in their proper relation to the somites in C. In all the older stages, centra of vertebrae as seen in sagittal sections are used as index of metameric level.

Abbreviations Au, auditory vesicle, C 1, first cervical (somite or vertebral primordium), Oc 1, first occipital somite, Oc B, primordium of basal portion of occipital bone, L, lumbar, S, sacral, T, thoracic

hernia A diaphragm, intact at birth, may subsequently be weakened locally and allow some of the abdominal viscera to protrude into the pleural cavity In such an event, however, the postnatal development of the condition is usually evidenced by the fact that the herniated viscera are covered by a distended sac of diaphragmatic peritoneum

There may, of course, be herniation of the abdominal viscera at locations other than through the diaphragm The most common points of weakness in

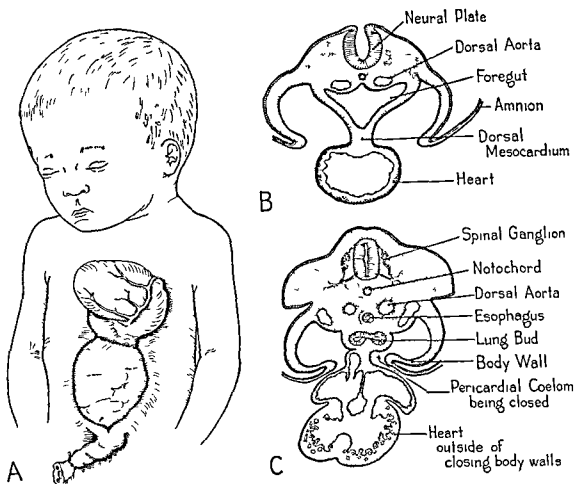


FIG 307 Ectopia cordis A, Sketch of an infant with ectopia cordis and incompletely closed abdominal wall B, C, Hypothetical cross-sectional diagrams of embryos at two critical stages to suggest probable manner in which this abnormality arises

the abdominal wall are in the umbilical and inguinal regions Umbilical hernia will be considered later in this chapter with other abnormalities of the position of the gut-tract and mesenteries Inguinal hernia will be considered in the chapter on the urogenital system in connection with the development of the scrotal pouches

The pericardium as well as the diaphragm may be the site of defective development A radical defect which does not permit long survival after birth is known as *ectopia cordis* (Fig 307, A) No embryos showing critical stages in the development of this defect have been described, but from the nature of the malformation as it has been seen repeatedly in newborn infants one can speculate fairly shrewdly as to the general manner in which develop-

Abnormalities in Development of Body Cavities One of the interesting developmental abnormalities from a clinical standpoint is a *congenitally incomplete diaphragm*. In such a case the defect—for some unknown reason more usually on the left side—is most often due to faulty development of the pleuro-peritoneal fold (Fig 306, B). The abdominal viscera tend to herniate through this opening in the diaphragm into the pleural cavity (Fig 306, A), interfer-

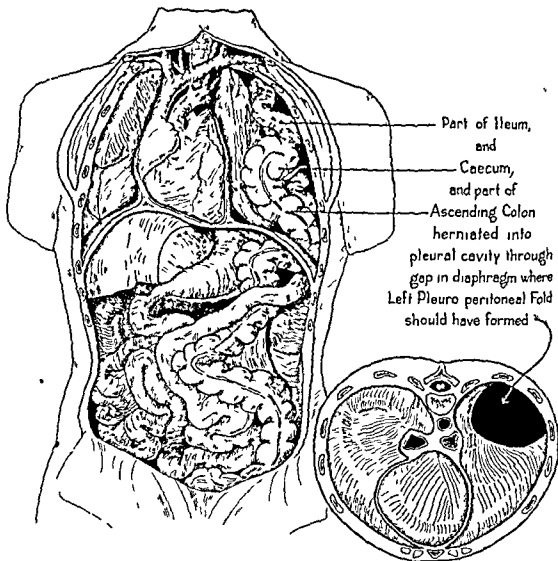


FIG 306 Diaphragmatic hernia (Partly after Arey) A, Ventral dissection showing intestines projecting into left pleural cavity B, Schematic drawing of thoracic face of diaphragm to show location of developmental defect involved

ing with the proper expansion of the lung and often putting indirect pressure on the heart as well. Surgical reduction of the hernia and repair of the gap in the diaphragm is usually possible in such cases. The dramatic establishment of normal conditions following such an operation is much more gratifying than the results of the palliative surgery which is the only recourse in many of the other types of congenital defects. In connection with such cases it should perhaps be mentioned that a congenital absence of part of the diaphragm is not the only condition which may lead to the occurrence of a diaphragmatic

between the liver and the stomach persists as the gastrohepatic omentum (lesser omentum, ventral mesogastrium), and the portion between the liver and the ventral body-wall, although reduced, persists in part as the falciform (ventral) ligament of the liver (Fig 308)

In contrast with the ventral mesentery, which eventually disappears except in the region of the liver, almost the entire original dorsal mesentery persists. It serves at once as a membrane supporting the gut in the body cavity and a

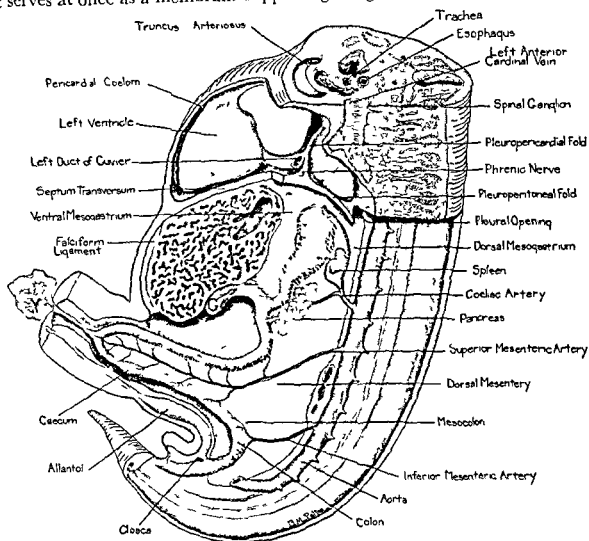


FIG 308 Lateral dissection to show arrangement of viscera and mesenteries in an embryo of about six weeks. In region of developing lungs body is cut parasagittally, well to left of mid-line, in order to show relations of pleuropericardial and pleuropentoneal folds. Below developing diaphragm, dissection has been carried to mid-line. Abbreviations Y, yolk-sac, G, gall bladder

path over which nerves and vessels reach the gut from main trunks situated in the dorsal body-wall. Its different regions are named according to the part of the digestive tube with which they are associated, as for example dorsal mesogastrium, that part of the dorsal mesentery which supports the stomach, mesocolon, that part of the dorsal mesentery supporting the colon. In attaining their adult relations the mesenteries undergo radical changes from their initial position in the sagittal plane of the body as they become involved in the elongation and foldings of the gastro-intestinal tract which they support.

ment must have departed from the normal. Unquestionably the defect must be established very early in development—probably about the third week. It is at this time that the demarcation between intra- and extra-embryonic coelom is being established by the folding off of the body. When the ventral body-walls in the cardiac region are being formed they must catch the heart outside their place of convergence somewhat as suggested in the hypothetical sectional diagrams of Fig. 307 B, C, rather than inside as occurs normally (Fig. 72). Whether the primary disturbance is something which causes the heart to protrude abnormally far ventrally, or whether it has something to do with the growth pattern of the body-walls is difficult to guess. Unfortunately, as with most of the congenital defects, we know the end-results and something of the steps by which they were arrived at but virtually nothing about the actual causative factors.

A defect of the pericardium that causes relatively little functional disturbance may occur as a result of a *defective pleuropericardial fold*. As is the case with the defects of the pleuroperitoneal folds involved in diaphragmatic hernia, this condition is more likely to occur on the left side. It leaves an open communication of varying size between the pericardial and one of the pleural cavities. Under normal conditions such a defect causes little disturbance and may go unnoticed unless there is an otherwise inexplicable spread of a pleural infection into the pericardial region.

MESENTERIES

Having traced the way the regional divisions of the body cavities are established, we may now turn our attention to the manner in which the mesenteries attach the viscera in the peritoneal cavity. As was the case in dealing with the coelomic cavities, it will be well before discussing the later changes to review some of the basic relations in young embryos.

Primary Mesentery The same folding process that separates the embryo from the extra-embryonic membranes completes the floor of the gut (Figs. 70, 71). Coincidentally the splanchnic mesoderm of either side is swept toward the mid-line enveloping the now tubular digestive tract. The two layers of splanchnic mesoderm which thus become apposed to the gut and support it in the body cavity are known as the primary or common mesentery. The part of the primary mesentery dorsal to the gut, suspending it from the dorsal body-wall, is the dorsal mesentery. The part of the primary mesentery ventral to the gut, attaching it to the ventral body-wall, is the ventral mesentery (Fig. 299, D). The primary mesentery, while intact, keeps the original right and left halves of the coelom separate. But the more caudal part of the mesentery ventral to the gut very early breaks through, bringing the right and left coelom into confluence and establishing the unpaired condition of the body cavity characteristic of the adult (Fig. 299, F).

In the region of the liver the ventral mesentery persists and the liver arises, as we have seen, from an outgrowth of the gut which in its development pushes into the ventral mesentery (Fig. 299, E). The portion of the ventral mesentery

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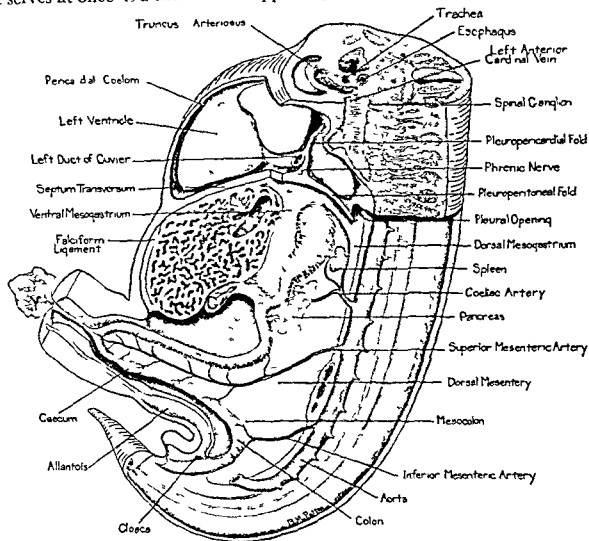


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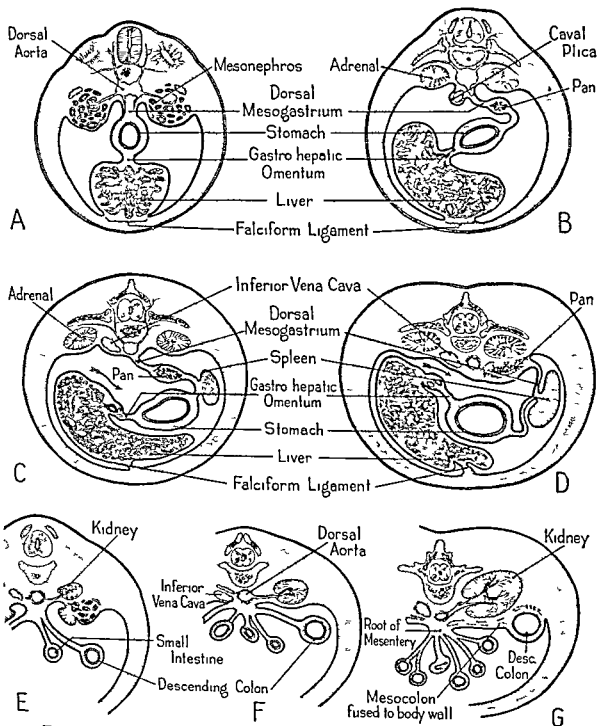


FIG 310 Cross-sectional plans of developing body to show changes in relations of mesenteries (Adapted from several sources) A-D, Sections at level of stomach and liver to show formation of omental bursa E-G, Sections at level of kidney to show fusion of parts of mesocolon to body wall This illustration should be studied in comparison with Fig 309, which shows corresponding stages in frontal plan

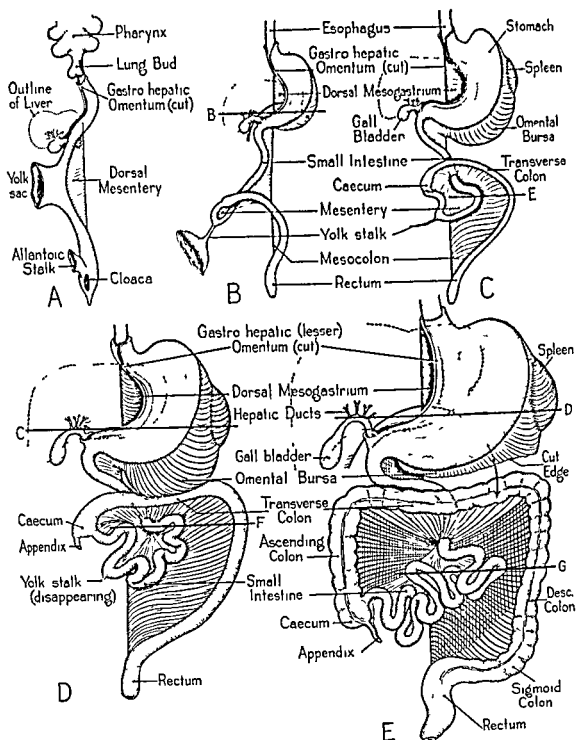


FIG 309 Frontal view plans schematically summarizing major developmental changes in position of gut and in relations of mesenteries (Adapted from a number of sources) Heavy horizontal lines, identified by letters, indicate locations of cross-sections designated by same letters in Fig 310 Cross-hatched areas in E indicate the part of mesentery of the duodenum and the parts of the mesocolon which become fused to body-wall (Cf Fig 310, G)

the distinction between these two parts of the lesser peritoneal space is not necessarily emphasized. In this event the term omental bursa is likely to be used [somewhat loosely] as synonymous with the lesser peritoneal sac.

The entrance from the main peritoneal cavity into the lesser peritoneal sac is known as the *epiploic foramen* (foramen of Winslow). In young embryos the epiploic foramen is a rather broad opening into the developing lesser sac. As development progresses it becomes much more restricted (Figs 311, 312, B-D, 313). To grasp the relations of the epiploic foramen, certain fundamental conditions already dealt with in other connections should be clearly in mind

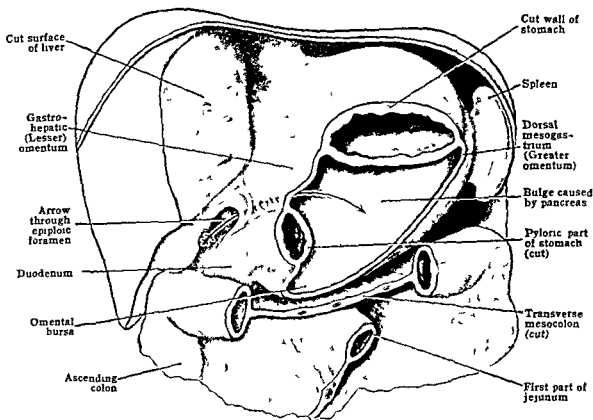


FIG 311 Dissection to show relations of developing omental bursa (Redrawn, with slight modifications, from Arey "Developmental Anatomy," courtesy, W B Saunders Co)

It will be recalled that an undivided peritoneal cavity is first established when the ventral mesentery caudal to the level of the hepatic diverticulum breaks through and places the originally paired coelomic chambers in communication with each other (Figs 299, F, 308). We have just seen how the lesser peritoneal space is formed by the departure of the stomach from its primary sagittal position and the accompanying sacculization to the left of its supporting membranes. Consequently, to pass a flexible probe from the main (greater) portion of the peritoneal cavity into the lesser sac, it would be necessary to direct it first cephalad on the right side of the ventral mesogastrium. It would then have to curve to the left behind the stomach and pass into the bursa in the pouched-out dorsal mesogastrium. (See arrows in Figs 302, 309, B)

Later Changes in Relation of Mesenteries In a sense the supporting tissue about the esophagus is comparable to a primitive mesentery-like support which never becomes thinned into a membrane. It will be recalled that this region becomes modified in the formation of the dorsal part of the mediastinum. In the gastric region the changes in the associated part of the dorsal mesentery are set in motion along with the changes in position of the stomach itself. We have seen that the cardiac end of the stomach is shifted to the left while its pyloric end moves to the right, and that this change in axial direction is accompanied by rotation (Fig. 275). Inevitably the dorsal mesogastrium must be extended with these changes. Its expansion, however, is far greater than necessary merely to accommodate itself to the positional changes of the stomach. It forms a large sac which soon begins to protrude to the left of the stomach, well beyond its greater curvature (Figs. 309, B-D, 310, B-D). The cavity within this increasingly voluminous pouch formed by the dorsal mesogastrium is usually called by anatomists the *omental bursa*. In adult anatomy the dorsal mesogastrium itself is commonly called the *greater omentum*, in distinction to that part of the ventral mesentery between the stomach and the liver (gastrohepatic omentum) which is designated as the *lesser omentum*.

As the greater omentum with its contained bursa continues to extend beyond the greater curvature of the stomach, the concomitant change in the axial position of the stomach causes the bursa to grow increasingly in a caudal direction (Fig. 309, B-D). In so doing the greater omentum soon encounters the transverse mesocolon (Fig. 311) by which it is deflected ventrally to hang over the transverse colon and cover, like an apron, the underlying coils of the small intestine (Fig. 312, C, D). It is not long after it is established in these relations before the layer of the dorsal mesogastrium which has come to lie against the transverse mesocolon fuses with it to form a common supporting membrane (Fig. 312, C, D). Coincidentally the two layers composing the dependent part of the bursa fuse with each other to obliterate the distal part of the lumen of the bursa (Fig. 312, D). Later, when fat begins to be laid down in the body, this omental apron becomes one of the important sites of fat storage and at the same time provides an insulating layer protecting the abdominal viscera.

The entire bay of the peritoneal cavity which is formed dorsal to the stomach and bounded by its mesogastria is often called the *lesser peritoneal space*. For descriptive purposes we may recognize the omental bursa proper as that part of the bay bounded by the stomach and the dorsal mesogastrium (Fig. 311). The so-called "vestibule" is bounded by the stomach, the ventral mesogastrium, and the dorsal body-wall. In young embryos there is a recess of the vestibule extending cephalad between the right lung and the mediastinum sometimes referred to as the *infracardiac bursa* (Fig. 294). The distal part of this space is soon cut off by the developing diaphragm. In the adult traces of its lower part may persist as the *infracardiac recess* of the vestibule. Because of the direct continuity between the vestibule and the omental bursa proper,

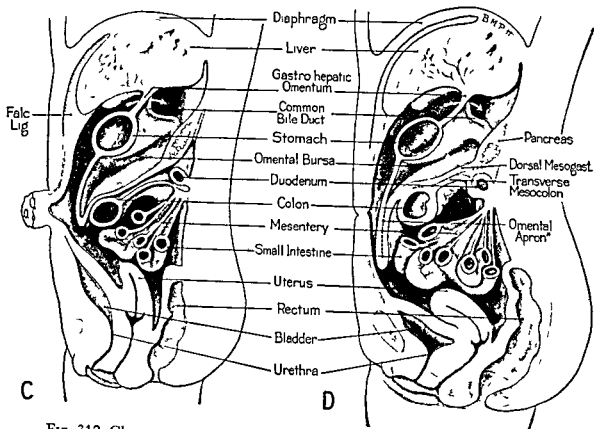
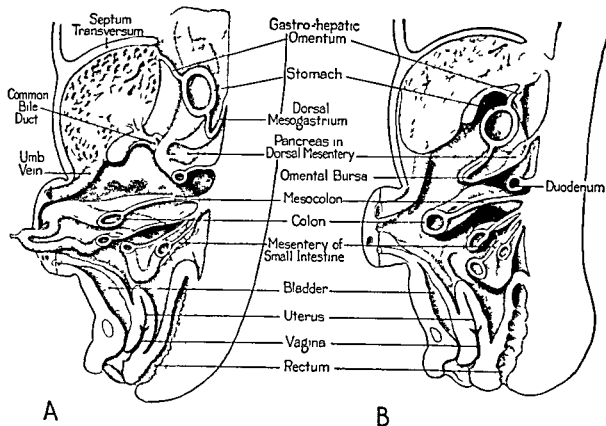


FIG 312 Changes in mesenteric relations as seen in schematized longitudinal sections of body A-C, Embryonic and fetal stages D, Adult (Adapted from a number of sources) White arrows in C and D pass through epiploic foramen

Another basic relation to keep in mind is the way the duct system of the liver and gall-bladder, and the accompanying blood vessels lie in the caudal border of that part of the ventral mesentery which persists. This group of ducts and vessels is sometimes collectively spoken of as the "hepatic root." The part of the mesentery that invests them is called the duodenohepatic ligament. It is, of course, the part of the original ventral mesentery just caudal to, and directly continuous with, the gastrohepatic omentum. Ordinarily the term lesser omentum is used to cover both the duodenohepatic ligament and the gastrohepatic omentum, and the more specific terms are used only when it is desired to emphasize local relations.

If one bears in mind the foregoing basic relationships in the development of the entrance from the greater to the lesser peritoneal sac, the adult anatomy of this region should be much more easily grasped. One sees in the epiploic foramen merely a communication from the main peritoneal cavity to the omental bursa. This communication must of necessity pass to the right of the hepatic root in the border of the ventral mesentery in order to reach the deep bay formed behind the stomach. (See arrows in Figs 309-312.) The way the pyloric end of the stomach and the duodenum bend backward toward the dorsal body-wall, and the expansion of the liver to the right and dorsally, both operate to reduce the relative size of the original communication (Fig 310, B-D, 312, B-D). In the adult (Fig 313) the foramen, though quite variable, ordinarily admits but two fingers without undue stretching. In the event of unexpected hemorrhage from the cystic artery in the course of surgical work in the region of the gall-bladder this foramen is a valuable point of orientation. An index finger slid into the epiploic foramen serves as an easy tactile guide for locating and compressing the hepatic artery.

The development of the omental bursa is involved with the growth of certain other structures in a manner which establishes a number of adult anatomical relationships very difficult to understand except in the light of their developmental history. Important among the structures concerned are the spleen, the pancreas, and the mesentery of the duodenum. The spleen starts to form within the dorsal mesogastrium when the stomach is still in its early phases of rotation. It grows rapidly and bulges more and more out of the left face of the mesogastrium (Fig 310, C). As the greater omentum (dorsal mesogastrium) grows, the spleen is carried dorsolaterally to lie close against the body-wall to the left of the stomach and a little dorsal to it (Fig 310, D). Although the spleen, along with the stomach, is carried caudad in the body from its point of origin, it remains beneath the ribs and, consequently, unless it becomes abnormally enlarged, it is difficult to palpate on physical examination.

The pancreas starts to develop between the two layers of the primary dorsal mesentery at duodenal level (Fig 299, E), but it soon extends cephalad into the part of the dorsal mesentery supporting the stomach (Fig 310, C, 312 A, B). The same growth process which we have just seen bringing the spleen into its definitive position swings the part of the dorsal mesogastrium

314), covered by a reflected layer of peritoneum which represents the original right face of the dorsal mesogastrium (Figs 310, A-D, 312, B-D)

The duodenum like the rest of the enteric tract at first has its own part of the dorsal mesentery (Fig 308) As the stomach rotates the duodenum is

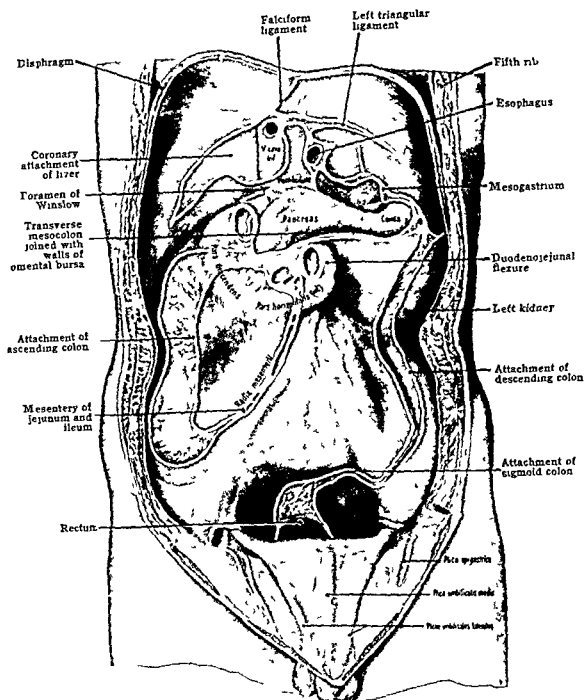


FIG 314 Definitive lines of attachment of mesenteries to dorsal body-wall and diaphragm (After Rauber-Kopsch, slightly modified)

brought closer to the dorsal body-wall and the mesoduodenum becomes greatly shortened (Cf Fig 312, A, B) Except for a small part immediately adjacent to the stomach, the duodenum soon comes to lie against the dorsal body-wall and its already reduced mesentery is completely resorbed (Fig 312, C) Nor do the changes in relations stop with the loss of its mesentery In

containing the pancreas against the dorsal body-wall (Fig 312, C, D) Shortly after this position has been attained the part of the dorsal mesogastrium in contact with the parietal peritonium fuses with it (Fig 310, D)

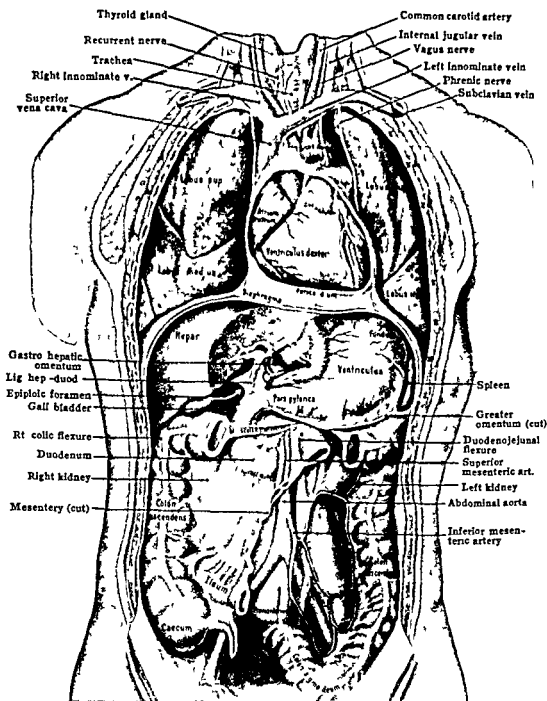


FIG 313 Ventral dissection to show relations of pericardial pleural and peritoneal cavities of adult (After Rauber-Kopsch) Most of the small intestines, part of the liver, and a segment of the transverse colon have been removed in order to show position of remaining viscera more clearly

During the third and fourth month this fusion becomes progressively more extensive until practically the entire length of the pancreas is involved. The pancreas eventually becomes tightly adherent to the dorsal body-wall (Fig

Abnormalities in Development of Mesenteries and in Visceral Position From the sixth until somewhere around the end of the ninth week of development the gut normally protrudes through the umbilical ring into the belly-stalk (Figs 273, 274, A, 364) It is usually in embryos of about 40 to

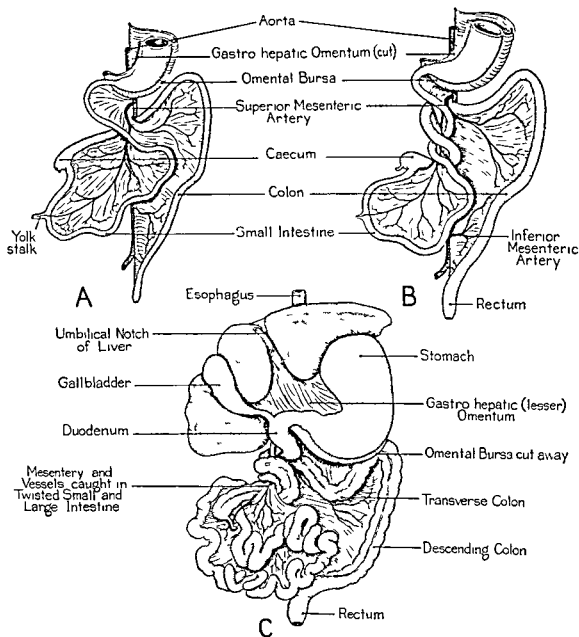


FIG 316 A case of volvulus and manner in which it probably originated (Redrawn, slightly schematized, after Dott, *British Jour Surg*, Vol 11, 1923-4) A, Reversed rotation of primary gut loop so small intestine passes ventral to transverse colon instead of dorsal to it as is normally the case (Cf Fig 309, B-D) B, Twisting of gut as it occurs following initial abnormal direction of rotation and abnormal crossing shown in A Note involvement of superior mesenteric artery C, Case of volvulus in a newborn infant which may well have arisen developmentally as indicated in hypothetical figures A and B

45 mm in crown-rump length (first half of tenth week) that one first finds the last of these protruding intestinal loops withdrawn into the peritoneal cavity (Fig 274, B) An *umbilical hernia* (Fig 315) may appear congenitally as the result of the persistence of this embryonic phase of intestinal protrusion

its new position against the dorsal body-wall the duodenum is in the angle between the transverse mesocolon and the more dorsal part of the mesogastrium cephalically (Fig 312, D) These layers, especially the mesocolon,

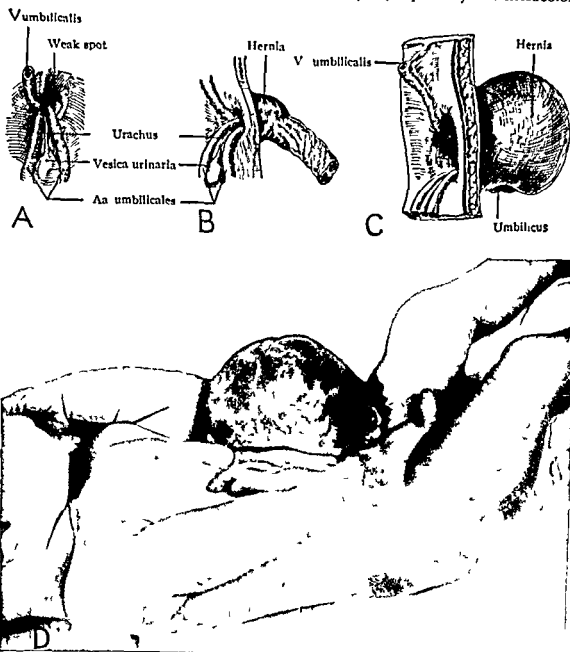


FIG 315 Umbilical hernia A-C, Diagrams showing point of weakness in developing abdominal wall and manner in which hernia is formed (From Callander, after Cullen "Diseases of the Umbilicus," courtesy, W B Saunders Co) D, Photograph of newborn infant with an extensive umbilical hernia (Courtesy, Dr Ernest H Watson)

cover the original peritoneal investment of the duodenum which is eventually resorbed altogether. Thus the duodenum finally lies embedded against the dorsal body-wall covered ventrocaudally by a secondarily acquired peritoneal reflection formed by the proximal part of the transverse mesocolon (Figs 312, D, 313)

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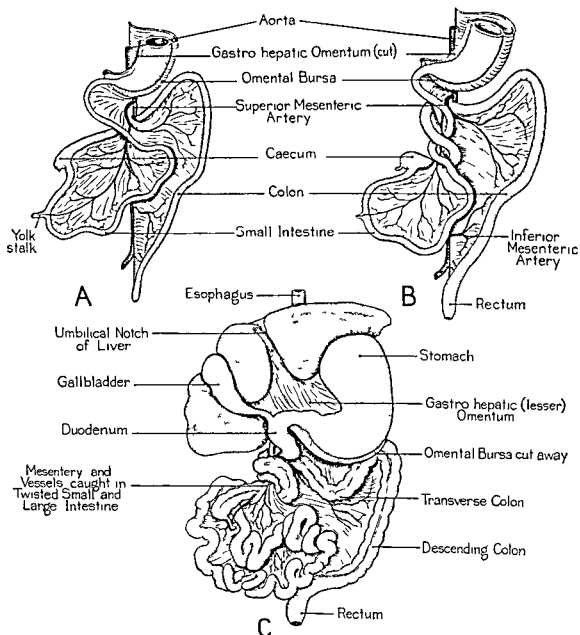


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Ductless Glands and Pharyngeal Derivatives

The various hormone-producing organs which are ordinarily spoken of as the ductless glands are comparatively small in size, and are located as isolated structures in widely separated places in the body. They do not constitute a coherent anatomical system with obvious structural interconnections such as those joining the widely separated parts of the nervous system or the lymphatic system. Because of the way they develop individually in early association with a variety of other organ systems, it would be quite logical to consider each endocrine gland in connection with the part of the body in which it arises. Such a procedure would, however, have the disadvantage of introducing digressions into a number of otherwise coherent stories. Moreover, there is an extraordinary interlocking of the regulatory functions carried out in the body by the various endocrine glands which gives the group a physiological coherence in spite of their morphological independence.

It seemed preferable, therefore, to devote a chapter to some of the major internally secreting glands as a group, although such a handling of their development must be regarded frankly as an arbitrary method of convenience. Such a chapter must also stop far short of completeness since several important hormones are produced by multiple small clusters of cells scattered in the substance of an organ with some other major function as, for example, the islets of Langerhans in the pancreas which produce insulin, a hormone concerned with sugar metabolism, or the interstitial cells in the testes which produce a male sex hormone. It would be cumbersome and repetitive to attempt to treat such endocrine areas except in connection with the organs in which they are located. Then, too, there are organs producing a hormone which can be recognized by its physiological effect, although we do not yet know the specific cells which produce it. Such is the situation with the hormone secretin formed somewhere in the intestinal walls and activating the pancreas. Obviously discussion of this type of internally secreting mechanism must be left, for the present at least, to physiology.

From the standpoint of sequence it makes little difference which of the endocrine organs is considered first. The appearance of its primordia in very young embryos makes the hypophysis a logical starting point. The thyroid and parathyroids also claim early attention. Their origin from specific areas of pharyngeal epithelium makes it necessary to review the morphology of the developing pharynx in some detail. When the relations in the pharyngeal region are thus freshly in mind seems to be an opportune time to take up

certain other structures of pharyngeal origin such as the thymus and the tonsils. This again must be regarded as merely a move of convenience, as the tonsils have no endocrine function and, although many workers have suspected the thymus of acting as a ductless gland in young individuals, its functions are not at all well understood at the present time. After this digression, attention must be focused on an entirely different region of the body for consideration of the adrenal gland. This, in brief, is the rationale for putting together in this chapter material which at first glance might seem illogically associated.

Development of the Hypophysis The hypophysis is formed from two separate primordial parts which unite secondarily. One of these primordia, known as Rathke's pocket, is an extension of the stomodaeal depression. This ectodermally lined space, shaped somewhat like a glove finger, grows in the mid-line toward the infundibular process of the diencephalic floor. The primary relations of the structures involved are best seen toward the close of the fourth week, just before the oral membrane has been completely resorbed. At this time the position of origin of Rathke's pocket, external to the oral membrane, is clearly evident (Figs 56, 318, A, 321).

The other primordial part of the hypophysis is the infundibular process which is formed in the floor of the diencephalon. This tissue is also of ectodermal origin, but its histology, in keeping with its derivation by way of the neural tube, even at the outset differs from that of the epithelial portions derived from the lining of Rathke's pocket. Eventually, with very little change in its relations, the infundibular process comes to constitute the so-called *pars neuralis* of the adult hypophysis (Fig 318).

The later changes in the stomodaeal portion of the hypophysis are more striking and extensive. Rathke's pocket elongates and its blind end becomes closely applied to the infundibular process (Fig 318, B). By this time the cephalic tip of the notochord, which originally lay in contact with the infundibular process (Fig 56), has undergone regression (Fig 318, C). During this process the original stalk by which Rathke's pocket arose from the stomodaeum first becomes narrowed (Fig 318, B), and then loses its connection with the stomodaeal epithelium (Fig 318, C, D). Meanwhile, the originally shallow stomodaeal depression has been greatly deepened by the forward growth of the adjacent nasal and maxillary processes and mandibular arch. A vivid picture of the extent of this deepening process can be obtained by comparing the original superficial location of Rathke's pocket (Fig 318, A) with the location of the line along which its stalk may be seen regressing in older embryos (Fig 318, C), and finally with the location at which unresorbed remnants of the stalk may appear in the adult (Fig 320).

As the stomodaeal portion of the hypophysis becomes molded into a double-layered cup about the *pars neuralis*, the rostral portion of its outer layer increases rapidly in thickness and takes on an obviously glandular appearance. In it we can now readily recognize the *pars distalis* (anterior lobe) of the adult hypophysis (Fig 318 C-E). The inner layer of Rathke's pocket

Ductless Glands and Pharyngeal Derivatives

The various hormone-producing organs which are ordinarily spoken of as the ductless glands are comparatively small in size, and are located as isolated structures in widely separated places in the body. They do not constitute a coherent anatomical system with obvious structural interconnections such as those joining the widely separated parts of the nervous system or the lymphatic system. Because of the way they develop individually in early association with a variety of other organ systems, it would be quite logical to consider each endocrine gland in connection with the part of the body in which it arises. Such a procedure would, however, have the disadvantage of introducing digressions into a number of otherwise coherent stories. Moreover, there is an extraordinary interlocking of the regulatory functions carried out in the body by the various endocrine glands which gives the group a physiological coherence in spite of their morphological independence.

It seemed preferable, therefore, to devote a chapter to some of the major internally secreting glands as a group, although such a handling of their development must be regarded frankly as an arbitrary method of convenience. Such a chapter must also stop far short of completeness since several important hormones are produced by multiple small clusters of cells scattered in the substance of an organ with some other major function as, for example, the islets of Langerhans in the pancreas which produce insulin, a hormone concerned with sugar metabolism, or the interstitial cells in the testes which produce a male sex hormone. It would be cumbersome and repetitive to attempt to treat such endocrine areas except in connection with the organs in which they are located. Then, too, there are organs producing a hormone which can be recognized by its physiological effect, although we do not yet know the specific cells which produce it. Such is the situation with the hormone secretin formed somewhere in the intestinal walls and activating the pancreas. Obviously discussion of this type of internally secreting mechanism must be left, for the present at least, to physiology.

From the standpoint of sequence it makes little difference which of the endocrine organs is considered first. The appearance of its primordia in very young embryos makes the hypophysis a logical starting point. The thyroid and parathyroids also claim early attention. Their origin from specific areas of pharyngeal epithelium makes it necessary to review the morphology of the developing pharynx in some detail. When the relations in the pharyngeal region are thus freshly in mind seems to be an opportune time to take up

makes contact with the pars neuralis and tends to fuse with it. The layer thus secondarily applied to the pars neuralis constitutes what is called the *pars intermedia* of the adult organ. Between the pars distalis and the pars intermedia there remains for a time a slitlike lumen which is appropriately called the *residual lumen* (Fig. 318, C-D) because it is all that remains of the original lumen of Rathke's pocket.

When the stomodaeal portion of Rathke's pocket has pretty well encased the distal end of the pars neuralis, a pair of lateral buds arise from the stomodaeal tissue. These are situated on either side of the infundibular stalk and tend to grow around it to meet and form a sort of collar about the neck of the stalk. This collarlike portion constitutes the *pars tuberalis* of the adult gland (Fig. 319).

Although mammals in general possess the same fundamental parts of the hypophysis there is considerable variation in some of the structural details.

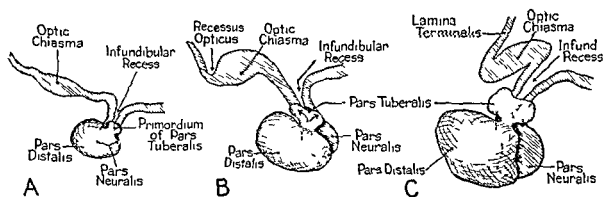


FIG. 319 Schematic diagrams showing origin of pars tuberalis of hypophysis

In many forms (e.g., cat, dog) the stomodaeal tissue extends much more around onto the caudal side of the pars neuralis than is the case in man. Such forms come to have a *pars intermedia* which envelops the pars neuralis fairly completely, rather than being limited to its rostral face as in man. There is also a great deal of variation in the extent of the residual lumen. In man it tends to become reduced to a vestigial slit which does not completely separate the pars distalis from the pars intermedia. In other forms the residual lumen gives a clean line of separation between these two parts of the hypophysis—a condition which is of great help in isolating them for the preparation of extracts for experimental purposes. Similarly in man and most of the land mammals commonly used experimentally, the *pars intermedia* has become so intimately adherent to the pars neuralis that their separation is difficult and uncertain. In the cetacea, however, enough connective tissue remains between Rathke's pocket and the infundibular process so that the *pars intermedia* can be readily and cleanly peeled away from the pars neuralis, even in the adult. This condition has proved very helpful in experimental work aimed at determining the nature of the hormones produced in each of the different parts of this complex and important ductless gland.

The histogenetic changes involved in the formation of the several parts of the hypophysis are best left for consideration in text-books of microscopical

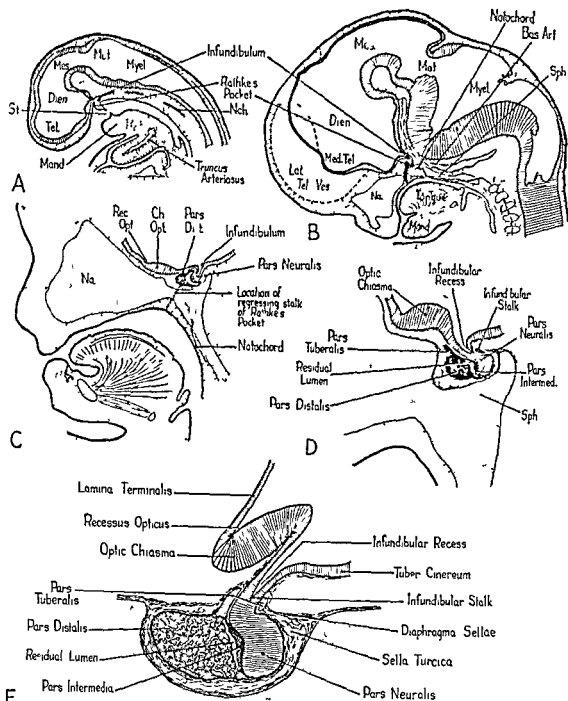


FIG 318 Diagrams showing changing relations of neural and stomodaeal portions of hypophysis during development A, Semischematic sagittal section of four-week (4-5 mm) human embryo B, Projection diagram of sagittal section of human embryo of about six and a half weeks (C-R, 15 mm, University of Michigan Coll, EH 4) C, Projection diagrams of sagittal section of human embryo of eighth week (C-R, 25 mm, University of Michigan Coll, EH 33) D, Sagittal section of hypophyseal region of embryo of eleventh week (C-R, 60 mm, University of Michigan Coll, EH 23) E, Schematic plan of adult hypophysis

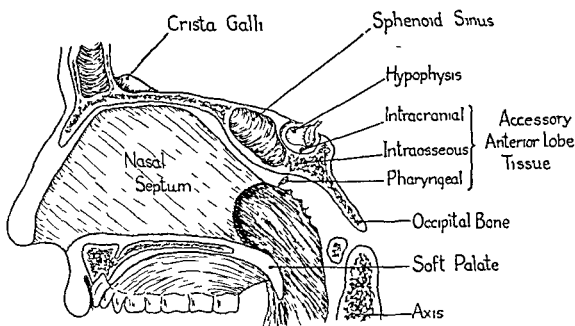


FIG. 320 Diagram to show manner in which accessory anterior lobe tissue of hypophysis may occur along old path of ingrowth of Rathke's pocket (Modified from Morris "Human Anatomy") Three possible locations are shown (1) "intracranial," i.e., within sella turcica, (2) "intraosseous," i.e., in sphenoid bone, and (3) "pharyngeal," i.e., in soft tissues of dorsal wall of pharynx

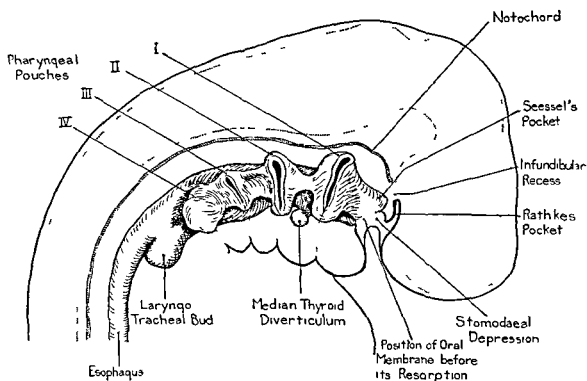


FIG. 321 Pharynx of a 4-mm (fourth week) human embryo with its relations to important adjacent structures indicated. Contours of visceral arches are suggested and broken lines between them show location of external gill furrows (cf Fig 53)

anatomy Suffice it to say, here, that in all the parts of the gland of stomodaeal origin the endocrine character of the tissue is early indicated by the way a rich sinusoidal circulation develops among the cords and nests of secretory cells. Each part has its own characteristic histology, and a great amount of careful work is being done currently with a variety of special staining techniques designed to secure evidence as to the specific source of certain of the hormones produced within this extraordinarily versatile gland. Much, however, remains to be found out before one can be very explicit about the five to eight or more hormones said to be produced in the hypophysis. It seems probable that when the active principles which produce these physiological effects are isolated they will prove to be fewer in number than currently believed. Some of the responses elicited experimentally and now attributed to specific hormones seem quite likely to prove to be combination effects. However this may work out, the formation of growth-promoting hormones and gonadotropic hormones in the pars distalis is established beyond question, and should be mentioned here because of the direct importance of these hormones in problems coming into the field of embryology. Two substances have been extracted from the pars neuralis, pitressin which raises blood pressure and exerts an antidiuretic effect, and pitocin which is a powerful activator of smooth muscle. It is the presence of the latter principle in the crude extract of the neural portion of the hypophysis which has made it so valuable in obstetrics in the induction of uterine contractions.

Abnormalities of the Hypophysis Functional disturbances in the amount or quality of one or more of the hormones produced in the hypophysis are not uncommon. Involving as they frequently do profound disturbances in growth, or in the normal development of the sex organs, they are of great clinical interest. Unfortunately, not enough is yet known concerning these functional disturbances to permit us to say whether they are hereditary or are the result of disturbances during development which do not manifest themselves as obvious morphological defects in the gland.

The commonest evident structural abnormality of the hypophysis is the presence of ectopic anterior lobe tissue along the course of ingrowth of Rathke's pocket. As indicated in the schematic diagram of Fig. 320, there are three locations in which these accessory masses of anterior lobe tissue may occur: (1) Within the depression (sella turcica) in the sphenoid bone in which the hypophysis lies, but outside the capsule of the gland, (2) within the substance of the sphenoid bone, and (3) in the soft tissues of the dorsal wall of the pharynx. The last location is by far the most common one, in fact, some writers feel that accessory anterior lobe tissue in the pharyngeal wall is such a usual occurrence that it should be regarded as a variant of the normal rather than as an anomaly.

Embryonic Pharynx Before considering the development of the specialized structures arising from pharyngeal epithelium, it is desirable to have the topography of the embryonic pharynx clearly in mind. It will be recalled that the part of the foregut just caudal to the oral membrane becomes com-

foramen cecum (Fig 251) Once freed from its parent epithelium the thyroid primordium migrates caudad, along a path ventral to the pharynx By the early part of the seventh week it lies at about the level of the laryngeal primordium (Fig 323) By far the greater part of its bulk now consists of lobes extending to either side of the mid-line with only a narrow isthmus of tissue joining them medially

Meanwhile, on the caudal face of the fourth pharyngeal pouches, there have been developing small diverticulac known by various names according to one's interpretation of their significance Some observers regard them as rudimentary fifth pharyngeal pouches Others are so firmly convinced that these small pouches join with the median thyroid primordium to form true

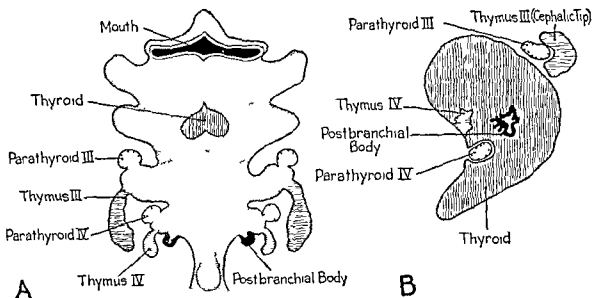


FIG 322 Schematic diagrams indicating origin and later interrelations of some of the derivatives of the embryonic pharynx (Modified from Swale-Vincent)

thyroid tissue that they prefer to call them lateral thyroid primordia Although the evidence in favor of this latter view seems to be increasingly strong, the noncommittal term designating these evaginations simply as postbranchial bodies is perhaps as useful as any until their significance is established beyond doubt All observers agree that the diverticulac in question break loose from the fourth pouch and become incorporated with the lateral lobes of the median thyroid primordium as it reaches posterior pharyngeal levels in its migration caudad (Figs 324, 325) Once associated with the thyroid lobes the tissue of postbranchial origin tends to become buried in them (Fig 322, B) and its subsequent history is difficult to follow The only question is whether, in this position within the thyroid, the postbranchial tissue actually gives rise to typical thyroid follicles or merely remains as a vestigial inclusion of unknown significance On this point additional work is needed

The histogenetic changes in the formation of the thyroid are comparatively simple to follow The primordial bud is composed of large columnar cells more or less radially arranged about a small lumen (Fig 326, A B)

pressed dorsoventrally and widened laterally to form the pharynx. The early structure of this part of the digestive tract clearly reflects its respiratory function in water-living ancestral forms. A series of four pairs of lateral bays of the pharyngeal cavity extend to either side forming the so-called pharyngeal pouches (Fig 321). Each pouch is opposite the corresponding gill furrow so that open gill slits are almost formed. Sometimes, even in mammalian embryos, there is actually a transitory break-through but usually a double-layered epithelial plate persists, composed of the ectoderm of the bottom of the gill furrow and the entoderm of the distal portion of the corresponding pharyngeal pouch. Most of the organs that are destined to arise from the pharyngeal epithelium have their primordial buds formed while the pharynx still shows this configuration reminiscent of its ancient gill-breathing condition. By the time the pharynx has been simplified to the condition characteristic of an adult air-breathing form, most of the pharyngeal derivatives have lost their original connections and migrated to positions more or less remote from their points of origin.

Relations of Cephalic End of the Notochord In the preceding section on the development of the hypophysis, mention was made of the primary fusion of the cephalic end of the notochord to the infundibular process (Fig 56). During the sixth week the notochord in this region undergoes regression, so that sagittal sections give the impression of its pulling away from the infundibular process and also losing its continuity (Fig 67). At this stage the relations of the notochord are quite variable. It usually lies free in the mesenchyme dorsal to the pharynx but may be found more or less intimately fused with Rathke's pocket or Scessel's pocket, or the roof of the pharynx farther caudally. Toward the close of the second month the mesenchymal concentrations constituting the primordium of the base of the skull surround the remains of the notochord back as far as the beginning of the spinal column (Fig 155). Usually the regressing notochord is caught in the sphenoid and basioccipital bones. Not infrequently, however, a portion of the notochord lies free of the developing cranium and bends ventrally into the pharyngeal wall (Fig 318, C). Secondary unions of the notochord with the pharyngeal epithelium occurring under these circumstances as well as those mentioned above show a curious tendency toward extreme cellular proliferation. Critical study of such areas of fusion might well prove fruitful in connection with a peculiar type of tumor which occurs in the retropharyngeal area and is known as a chordoma because it is believed to arise from notochordal tissue.

Thyroid Gland The thyroid gland is the earliest of the pharyngeal derivatives to make its appearance. In embryos toward the close of the fourth week a median diverticulum arises from the floor of the pharynx at a cephalocaudal level between the first and second pouches (Fig 321). Almost from its initial appearance this thyroid primordium is bilobed (Fig 322, A). It soon loses its connection with the floor of the pharynx, but its point of origin tends to remain marked by a depression of variable conspicuousness known as the

As these cells proliferate they become progressively smaller (Cf 326, A, B with C, D) This is a phenomenon which occurs quite generally in the differentiation of specialized tissues from their embryonic primordia (See, for example, Fig 143 on the histogenesis of connective tissue, and Fig 280 on the histogenesis of the epithelial lining of the esophagus) As the primary cellular mass expands it becomes arranged in cords with vascular mesen-

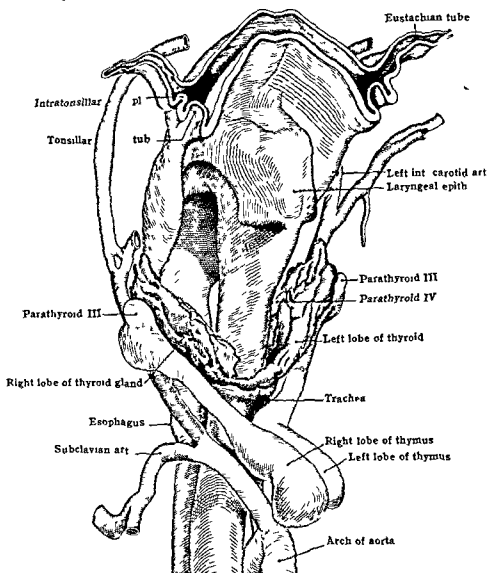


FIG 325 Reconstruction of pharyngeal region of a human embryo of 23 mm (middle of eighth week) to show migration of primordia of thymus, thyroid, and parathyroid glands toward their definitive positions (After Weller, Carnegie Cont to Emb, Vol 24, 1933)

chyme between them (Fig 326, C) During the third month, these epithelial cords break up to form cell nests surrounded by young, vascular connective tissue (Fig 326, D) To a slight degree toward the end of the third month (Fig 326, D), and more markedly during the fourth month (Fig 326, E) an acidophile material known as colloid begins to accumulate in the center of the cell nests When this occurs we have the characteristic thyroid follicle established with its central mass of colloid surrounded by a simple cuboidal or low columnar epithelium The later changes involve the accumulation of

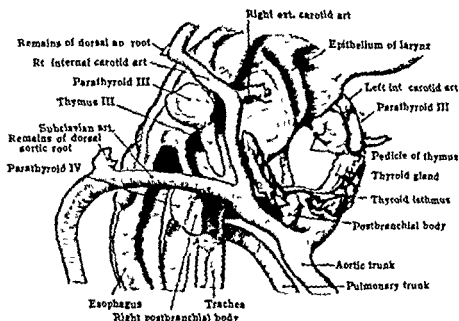


FIG. 323 Reconstruction of pharyngeal region of a human embryo of 14.5 mm (early in seventh week) to show origin of primordia of thymus, thyroid, and parathyroid glands (After Weller, *Carnegie Cont to Emb*, Vol 24, 1933)

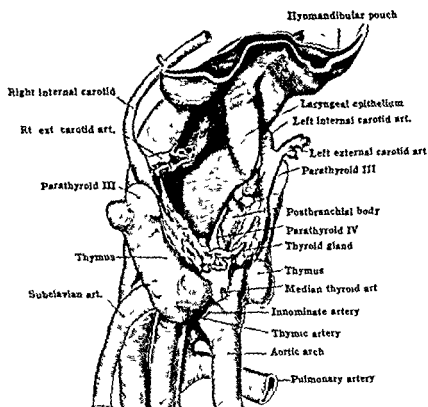


FIG. 324 Reconstruction of pharyngeal region of a human embryo of 16.8 mm (late in seventh week) showing an early stage in migration of thymic, thyroid, and parathyroid primordia (After Weller, *Carnegie Cont to Emb*, Vol 24, 1933)

As these cells proliferate they become progressively smaller (Cf 326, A, B with C, D) This is a phenomenon which occurs quite generally in the differentiation of specialized tissues from their embryonic primordia (See, for example, Fig 143 on the histogenesis of connective tissue, and Fig 280 on the histogenesis of the epithelial lining of the esophagus) As the primary cellular mass expands, it becomes arranged in cords with vascular mesen-

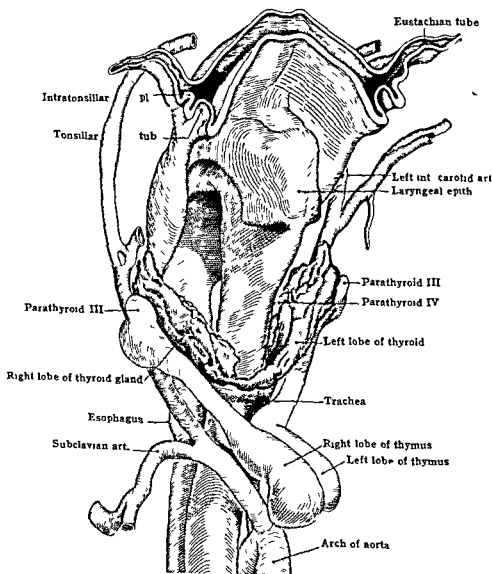


FIG 325 Reconstruction of pharyngeal region of a human embryo of 23 mm (middle of eighth week) to show migration of primordia of thymus, thyroid, and parathyroid glands toward their definitive positions (After Weller, Carnegie Cont to Emb, Vol 24, 1933)

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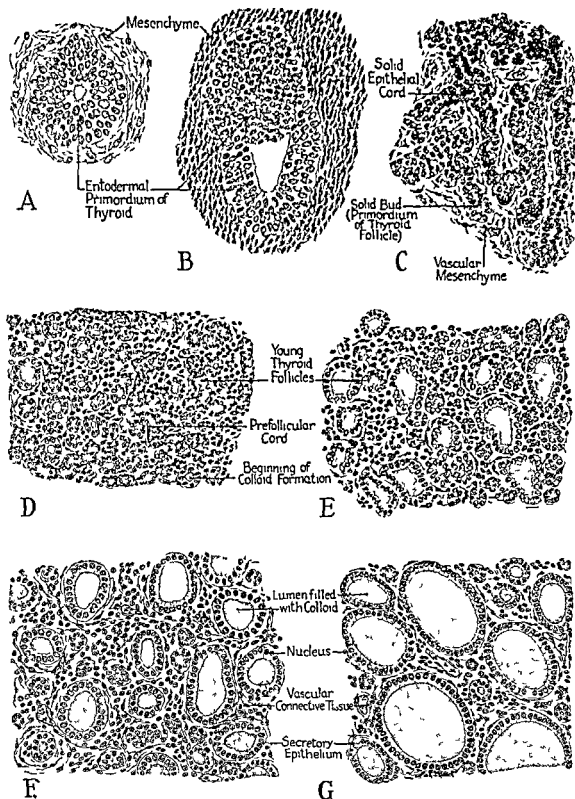


FIG. 326 Stages in histogenesis of human thyroid gland. Projection drawings ($\times 300$) from series in University of Michigan Collection. A, Four weeks (EH 36, 4.5 mm). B, Late in sixth week (EH 88, 11 mm). C, Middle of eighth week (EH 164, 25 mm). D, 11 weeks (EH 173, G, 65 mm). E, Fourteenth week (EH 145, G, 104 mm). F, 19 weeks (EH 143, F, 174 mm). G, Twenty-second week (EH 221, J, 200 mm).

greater amounts of colloid in increasing numbers of follicles, and the gradual differentiation of the surrounding embryonic connective tissue into the characteristic fibro-elastic tissue of the stroma of the adult gland. As is so characteristic of the ductless glands as a group, the connective tissue interspersed between the epithelial units is highly vascular providing an effective arrangement facilitating the entrance of the hormone into the blood stream.

Parathyroid Glands There are ordinarily two pairs of parathyroid glands formed. One pair is derived from the third and the other from the fourth pair of pharyngeal pouches. Because of their origin they are commonly designated as parathyroids III and parathyroids IV (Fig 322, A). Parathyroids III arise in close association with the thymic primordia (Fig 323). During the seventh week both these primordia are freed from the parent pouches and start to move caudad in association with each other. Although these two primordial cell masses become quite distinctly differentiated during the eighth week, parathyroids III are very likely to remain for a time attached to the young thymus or even become encased in its cephalic tip (Fig 322, B). With the further caudal migration of the thymus, parathyroids III are usually left embedded in the adjacent capsular tissue of the thyroid. They lie caudal to parathyroids IV, having passed them in their migration. Thus the cephalocaudal relations of the two pairs of parathyroids are reversed in the adult as compared with their position of origin in the embryo.

Parathyroids IV arise in close association with the postbranchial bodies, and when the postbranchial bodies merge with the lateral lobes of the median thyroid primordium, parathyroids IV usually become adherent to the thyroid capsule. Not infrequently they become more or less embedded in the substance of the thyroid gland (Fig 322, B).

The histogenetic changes are alike in the two pairs of parathyroids. Both start as solid cell masses on the craniodorsal aspect of the respective pharyngeal pouches. These cell masses break up into cords and nests with large, irregular capillary spaces (sinusoids) between them in the manner so highly characteristic of many of the ductless glands. The secretory cells show a rather pale clear cytoplasm. The oxyphile cells which are so striking in the adult gland are not differentiated until long after birth—ordinarily about the tenth year.

Thymus In mammals as a group, thymic tissue may arise either from the third or the fourth pharyngeal pouches, or from both. This situation has given rise to designating these primordia as thymus III and thymus IV. Thymus III is in most mammals the more important primordium. Thymus IV may be absent altogether and, even when formed, is likely to be quite rudimentary and give rise only to vestigial tissue masses. These masses usually become associated with the thyroid as it migrates caudad and may ultimately become actually embedded in its substance (Fig 322, B). In man thymus IV is so unimportant and inconstant that we may confine our attention to thymus III. In the following section, unless otherwise stated, all references to thymic primordia refer to thymus III.

The thymic primordia in man appear late in the sixth week as ventral outgrowths of the third pharyngeal pouches. They arise in very close association with the gill plate and many observers think that their primordial cell mass is contributed to by the ectoderm in the floor of the gill furrow as well as by pharyngeal pouch entoderm. When they first arise the thymic primordia have small cleftlike lumina, but these are soon lost. By the early part of the seventh week the primordia have elongated strikingly but they still retain their connection with the pharyngeal pouch and remain associated with parathyroid III (Fig. 323). During the seventh week they lose their lumen and increase rapidly in bulk. Their distal tips begin to approach each other as they swing toward the mid-line just caudal to the thyroid primordium (Fig. 324). By the middle of the eighth week all the pharyngeal derivatives have moved down in the neck (Fig. 325). The distal tips of the thymic primordia have made contact with each other and have started to slide down under the sternum into the mediastinum, where they lie in contact with the parietal pericardium. The fusion of the right and left thymic primordia usually remains superficial so that the organ never entirely loses its original paired character. The definitive position of the thymus is quite variable, but Fig. 330 gives a reasonable picture of its usual location in a young individual.

The histogenetic differentiation of the thymus is unusual in that after a start in one direction there is a radical change in the nature of the predominant tissue formed. To speak figuratively, it is as if the primordium suddenly changed its mind as to what it wanted to become. In its early stages, as one might expect from its epithelial origin, the thymus is made up of cords of closely packed cells looking much like the primordium of any young gland. During the third month, however, these epithelial cords tend to break up and form curious compact masses of cells known as thymic (Hassall's) corpuscles. In the fully differentiated condition of these corpuscles, some of their central cells tend to break down into a more or less amorphous mass which stains strongly with eosin. Outside this central mass, flattened epithelioid cells are wrapped, much like the layers of an onion. These curious spheroidal thymic corpuscles seem to be all that remain of the epithelial portion of the primordial thymus.

While these regressive changes have been taking place in the original epithelial primordia, there has been an abundant secondary ingrowth of mesenchyme which, by its increase in bulk, separates the epithelial remnants more and more widely. Late in the third month this interstitial tissue¹ begins to take on the characteristics of reticular connective tissue, and colonizing cells of a type destined to form lymphocytes (Fig. 391) settle in it. The rapid proliferation of these lymphoblasts with the resultant accumulation of lympho-

¹ Some authorities believe that this interstitial tissue arises by modification of some of the entodermal epithelial portion of the original outgrowths. It is true that modern experimental work is doing much to soften the old ideas of rigid specificity of germ layers in producing particular types of tissues; but, nevertheless, one can only remain instinctively skeptical about this isolated instance of the entodermal origin of connective tissue. Further work is needed on this extraordinarily interesting transformation in tissue type that occurs in the developing thymus.

cytes soon dominates the histological picture presented by the thymus so that it becomes very definitely a lymphoid organ rather than a young gland. In the final stages of its differentiation the thymus becomes lobulated and each lobule develops a cortical area of dense lymphoid tissue while a central portion (medulla) remains more diffusely populated with lymphocytes.

The histological characteristics described above for the thymus apply to fetuses approaching term and to young individuals. In the newborn (Fig. 329) the thymus has already become relatively very large (12–15 Gm). Its greatest

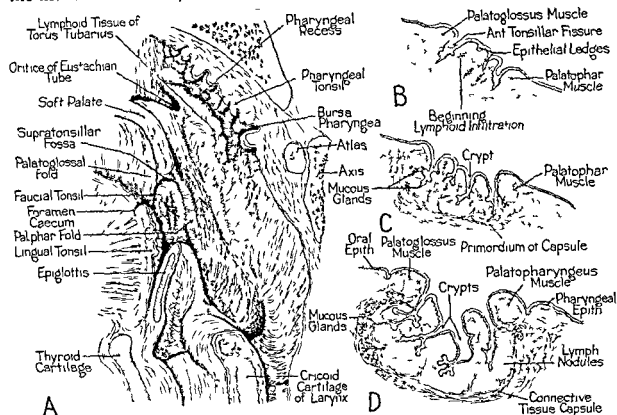


FIG. 327 A, Dissection of pharynx of an infant to show various tonsillar masses constituting Waldeyer's ring (Based in part, on Arey). Cut surfaces are in mid line, except soft palate, which has been cut to the right of the sagittal plane so uvula is removed, exposing faucial tonsil. B, C, D, Schematic diagrams showing three stages in development of faucial tonsils (Based, in part, on Miner, Arey, and Milton, Arch. Otolaryng., Vol. 25, 1937).

relative weight is not usually reached, however, until around two to four years of age. Its absolute maximum (30–40 Gm) is attained about the time of puberty. After puberty the lymphoid tissue of the thymus undergoes gradual regression, being replaced by fat (fatty involution), or by connective tissue (fibrous involution), or a combination of the two. Hassall's corpuscles persist with less change and the thymus of older individuals is very likely to consist of nothing more than clusters of these corpuscles with a minimal amount of adherent lymphoid tissue embedded in fat and fibro-elastic connective tissue.

Tonsils. When used alone the term tonsil ordinarily refers to one of the masses of lymphoid tissue on either side of the passage from the oral cavity to the pharynx. Technically these two masses are the palatine (faucial) tonsils (Fig. 328). There are other tissue masses of similar type which together with

the paired, laterally placed, palatine tonsils form a ring (Waldeyer's ring) of lymphoid tissue around the entrance from the oral cavity into the pharynx. Above, on the superior dorsal walls of the nasopharynx (Fig 327, A), is an extensive area heavily infiltrated with lymphocytes and containing many lymph follicles which collectively constitute the pharyngeal tonsil ("the

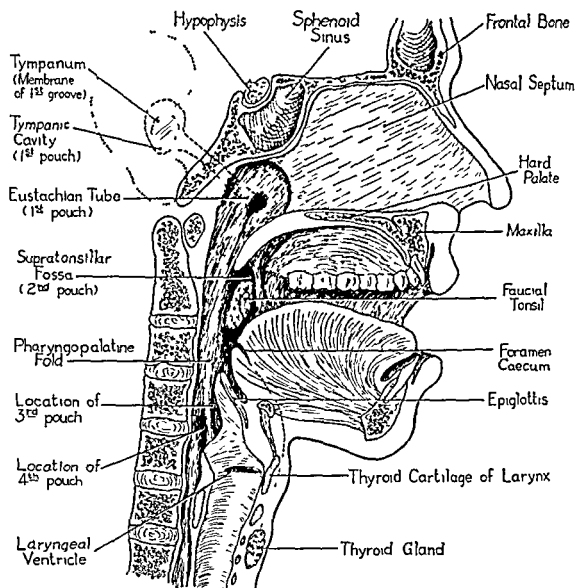


FIG 328 Schematic drawing of a median dissection showing locations, in adult, of vestiges of the pharyngeal pouches and certain of their derivatives (In part after Corning)

adenoids") On the floor of the oro-pharyngeal passageway, situated on the root of the tongue, is another aggregation of lymph follicles which constitute the lingual tonsil (Fig 327, A)

The palatine tonsil starts to form during the latter part of the third month with a lymphoid infiltration of the connective tissues about the regressing second pharyngeal pouch. As the lymphoid tissue increases in bulk the overlying epithelium grows into the lymphoid tissue in the form, at first, of

solid cellular ledges. These ledges gradually open up to form crypts extending into the tonsils (Fig 327, B, C). During the last trimester of development the lymphoid tissue becomes organized into definite follicles and the crypts branch, thus opening new, crooked passageways from the pharyngeal lumen deep into the substance of the growing tonsil (Fig 327, D). On the attached side of the tonsil the increasing mass of the lymphoid tissue compresses the connective tissue to form a partial capsule. Postnatally the tonsils continue to grow until they bulge out of the original cleft into the passageway from oral cavity to pharynx. There persists, adjacent to the cephalic pole of each tonsil,

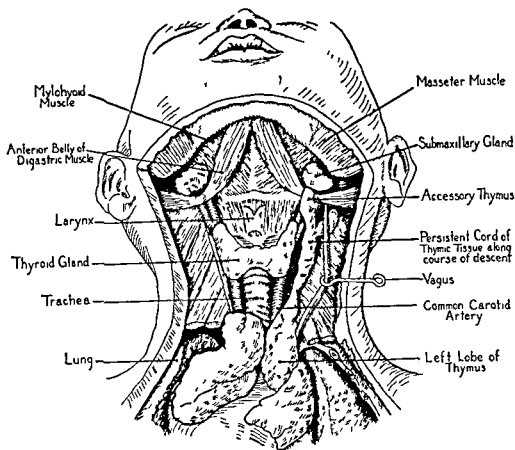


FIG 329 Persistent thymic tissue along course followed by left lobe of thymus in its descent (After Bien, from Corning)

a depression called the supratonsillar fossa (Fig 328) which is all that ordinarily remains of the once capacious second pharyngeal pouch.

The pharyngeal and lingual tonsils develop in a similar manner starting with a diffuse lymphoid infiltration that gradually becomes more extensive. They differ from the palatine tonsils in having their lymph follicles scattered over a less circumscribed area and in having much shallower and less complicated crypts.

Abnormalities of Pharynx and Pharyngeal Derivatives One of the most striking developmental defects of the pharyngeal region is a *cervical fistula*. In this anomaly a slender, epithelially lined tract extends from the lumen of the pharynx to open externally on the neck. Such a condition represents a persistent gill slit. Its internal relations and the level of the external

opening vary depending on which of the pharyngeal pouches was involved. Ordinarily it is the second or the third pouch and, in either case, the external opening will be found along the medial border of the sternocleidomastoid muscle. A fistula arising from the second pouch starts internally from the tonsillar fossa and usually makes its exit on the neck somewhere near the level of the larynx, whereas one from the third pouch leaves the pharynx below the level of the hyoid bone and usually reaches the surface near the base of the neck (Fig. 330). Defects of this type are readily recognizable when

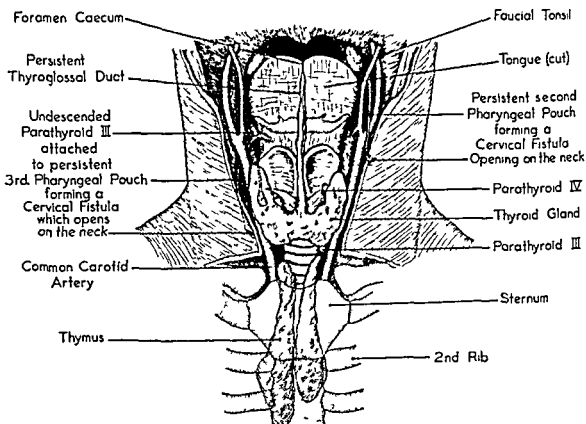


FIG. 330 Schematic diagram of a dissection of the neck with jaw removed (Modified after Braus from Fischel.) Root of tongue has been cut across to show a persistent thyroglossal duct. On the subject's right are indicated an undescended parathyroid III and the position characteristically occupied by a persistent third pharyngeal pouch opening on the neck as a cervical fistula. On the subject's left is indicated a cervical fistula associated with the second pharyngeal pouch.

they reach the surface, but when they are less extensive and exist only as pockets, or as mere epithelially lined cysts, they may pass unrecognized until they cause trouble by becoming infected or distended by the accumulation of fluid.

ANOMALIES OF THYMUS The commonest developmental irregularity involving the thymus is the persistence of cords of thymic tissue along the course followed by the gland in its descent. Such cords may be either unilateral (Fig. 329) or bilateral.

ANOMALIES OF THYROID GLAND Developmental disturbances of the thyroid gland may be of a number of types. As in other glandular structures there may

be functional defects not evidenced by any obvious structural departure from the normal, or a gland in the normal location may be significantly below normal size. If for any reason there is a marked deficiency in the amount of thyroid hormone produced, the individual will tend toward the cretin type—that is, be dwarfed in stature (Fig 131, G), sluggish intellectually, and possessed of a dry thickened skin.

Another type of defect encountered is retention of an epithelial connection between the thyroid and its original point of origin from the floor of the pharynx, a condition known as *persistent thyroglossal duct*. The epithelial tract may be open all the way from the foramen cecum to the larynx (Fig 330), or there may be a series of blind pockets (*thyroglossal duct cysts*) at intervals along the course of migration of the thyroid.

There are not infrequently small *accessory masses of thyroid tissue* which are difficult to distinguish from the parathyroid. As a matter of fact, it is often impossible to be certain of the character of such masses unless they are sectioned and studied microscopically.

ANOMALIES OF PARATHYROIDS The commonest of the developmental anomalies involving the parathyroid glands are variations in the extent of their migration with a resulting abnormality of location, and the presence of supernumerary parathyroids. Not uncommonly there are two or more aberrant parathyroids which may be found anywhere in the connective tissue adjacent to the thyroid or the thymus, or actually buried in thyroid or thymic tissue. The difficulty of telling small, accessory thyroid masses from aberrant parathyroids, and the fact that parathyroids III, or accessory parathyroids, may be carried down beneath the sternum by the thymus in its migration into the mediastinum, can combine to confront the surgeon with problems requiring resourcefulness and sound judgment based on a background of embryological knowledge.

Adrenal Gland and Accessory Chromaffin System The adrenal gland of mammals represents a secondary coalescence of two types of glandular tissue that occur quite independently in the fishes and are only loosely associated in amphibia and reptiles. Its embryological development in man suggests this history by the separate origin of its two parts—the centrally located medulla and the cortex which invests the medulla. The origin of the adrenal medulla is involved with the origin of a whole group of tissue masses of the same general type and potentialities. All of them are developed from certain cells of neural crest origin which migrate ventrally along with other cells entering the sympathetic ganglia but eventually detach themselves from the ganglia and become, not nerve cells, but gland cells active in the production of a specific hormone, epinephrin. Due presumably to the presence of this internal secretion or its precursor substance in their cytoplasm, they are stained brownish by chromic acid salts which has led to their designation as *chromaffin cells*. Clusters of these chromaffin cells become located in close proximity to each of the chain ganglia, and are known as paraganglionic chromaffin bodies, or more briefly as paraganglia (Fig 331). At birth the

paraganglia are approximately a millimeter in diameter. After birth they tend to become somewhat smaller but they remain recognizable in sections even in advanced years. Other masses of chromaffin tissue from the same

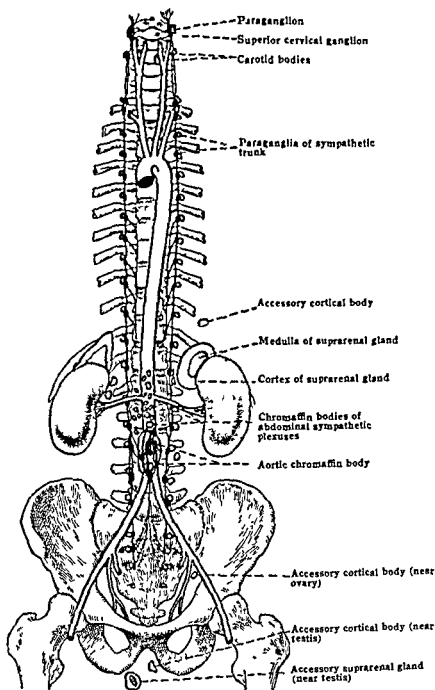


FIG 331 Diagram showing distribution of adrenal cortical and medullary tissue in the body (From Cunningham's "Anatomy," modified from Swale-Vincent, courtesy, Oxford University Press) The medullary (chromaffin) tissue is shown in orange, the cortical tissue in blue

source appear in various places retroperitoneally along the course of the aorta. Several small masses are usually present in the region of the abdominal sympathetic plexus, near the root of the inferior mesenteric artery (Figs 331, 334). Some of the larger and more caudally located of these masses form the

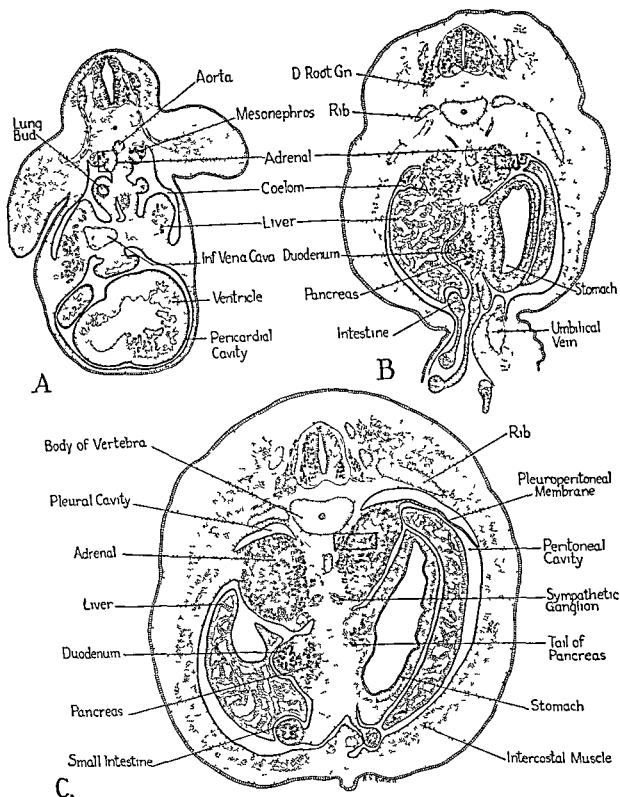


FIG 332 Topographical diagrams of sections at adrenal level of embryos at various ages A, Sixth week (EH 35, C-R, 9 mm) B, Seven weeks (EH 138, C-R, 17 mm) C, Eighth week (EH 164, C-R, 25 mm) Areas drawn at higher magnification in Fig 333 are indicated by rectangles

so-called *aortic chromaffin body* (lumbar paraganglionic mass, organ of Zuckerkandl) This aggregation of chromaffin tissue may retain its original paired condition, or fuse to form a single mass ventral to the aorta The largest and most constant masses of chromaffin tissue are those destined to form the *medulla of the adrenal* They appear on either side just cephalic to the develop-

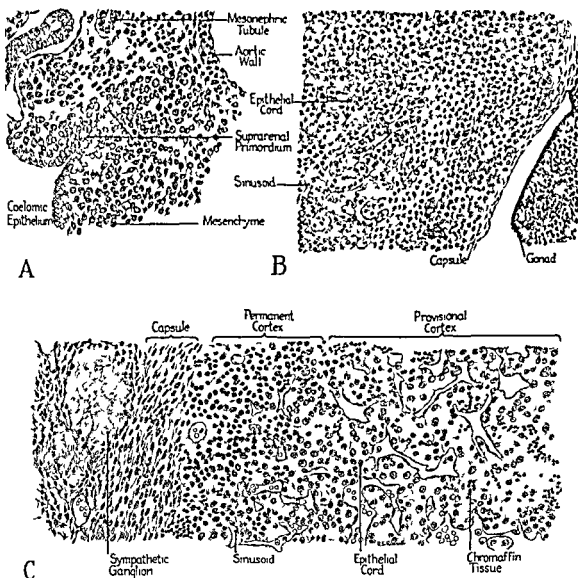


FIG 333 Stages in histogenesis of adrenal gland For location of areas drawn, see Fig 332 Projection drawings, $\times 200$ A, From a 9-mm embryo B, From a 17 mm embryo C, From a 25-mm embryo

ing kidneys, and in mammals become secondarily invested with a different type of tissue which forms the adrenal cortex

ADRENAL CORTEX The adrenal cortex arises from the splanchnic mesoderm at the base of the dorsal mesentery near the cephalic pole of the mesonephros In embryos of the sixth week a fissure can be seen in this region, where mesodermal cells appear to be proliferating rapidly and pushing into the underlying mesenchyme (Figs 332, A, 333, A) By the end of the seventh week a considerable mass of cells has accumulated (Fig 332, B) and they

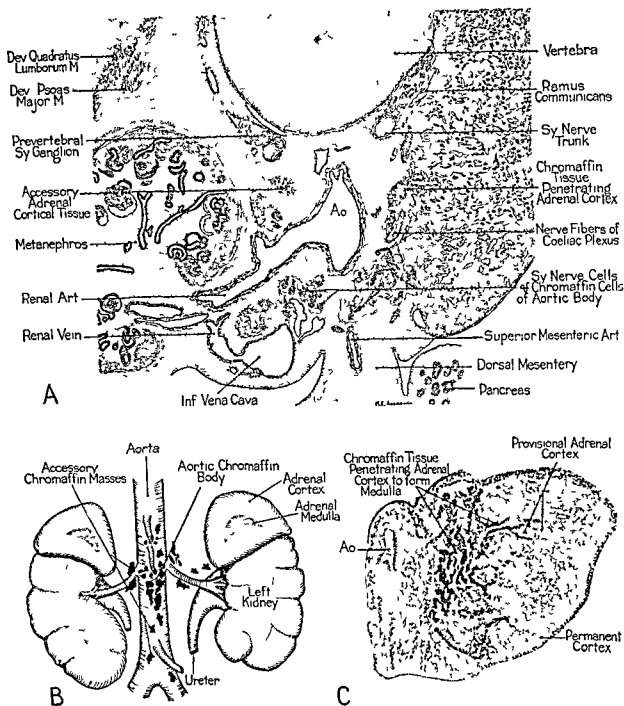


FIG 334 Development of adrenal medulla and accessory chromaffin masses
 A, Section ($\times 40$) of a human embryo of eighth week (C-R 25 mm), showing migration of chromaffin tissue to form aortic body and adrenal medulla. Section is cut somewhat on a slant so that kidney shows on left whereas adrenal appears on right. B, Schematic diagram showing accessory chromaffin masses identifiable in interrenal area of a six-month fetus (Modified from Iwanow, *Zeitschr f Anat u Entw*, Bd 84, 1927). C, Frontal section of adrenal of embryo of seventh week showing chromaffin tissue penetrating to form medulla of adrenal (After Wiesel, from McMurrich).

are already beginning to be arranged in cords with sinusoids between them (Fig 333, B) In embryos toward the close of the eighth week the cortical masses have attained considerable size (Fig 332, C) They are by this time free of the parent mesothelial layer and invested in a capsule of young connective tissue The cordlike arrangement of the secretory cells with sinusoidal vascular spaces between them has become quite striking (Fig 333, C)

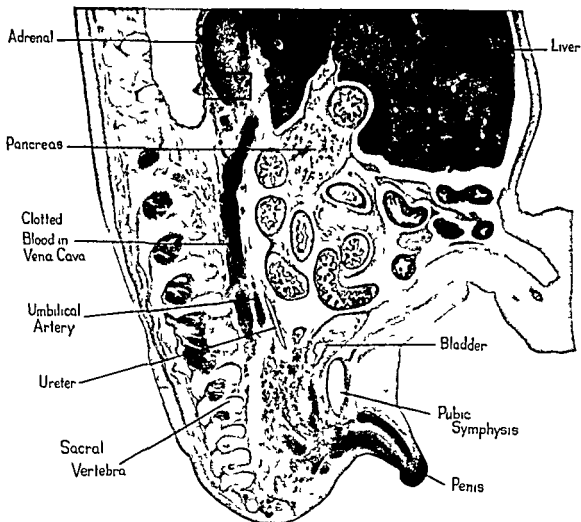


FIG 335 Photomicrograph ($\times 10$) of parasagittal section through cranial half of body of a nine week human embryo (University of Michigan Coll., EH 17, C-R, 39 mm) Small rectangle indicates portion of adrenal gland shown in high magnification in Fig 336

While the adrenal cortex has thus become a conspicuous landmark in the embryonic body (Fig 335), the development of medullary tissue has been progressing, although much less conspicuously Chromaffin cells which have migrated out of the adjacent sympathetic ganglia by way of the celiac plexus collect along the mesial border of each cortical mass and soon penetrate it so that areas of chromaffin cells constituting the primordial adrenal medulla gradually become encapsulated by the growing cortical tissue (Fig 334, A, C)

During the third month a curious differentiation occurs within the cortex The inner portion develops into quite mature-looking cell cords, and these

cells show vacuoles suggesting that they may already be active in secretion. This inner part of the cortex is called the "provisional cortex" (Fig 333, C, 336). Outside the provisional cortex is a zone of much less differentiated cells which constitute the so-called "permanent cortex." The implication of these names becomes clear only in the light of changes which carry over into the postnatal period. At the end of fetal life the permanent cortex shows little differentiation, and the provisional cortex, although relatively somewhat thinner than in young fetuses, still constitutes the bulk of the cortical portion of the adrenal. Beginning toward the close of gestation, and increasing in

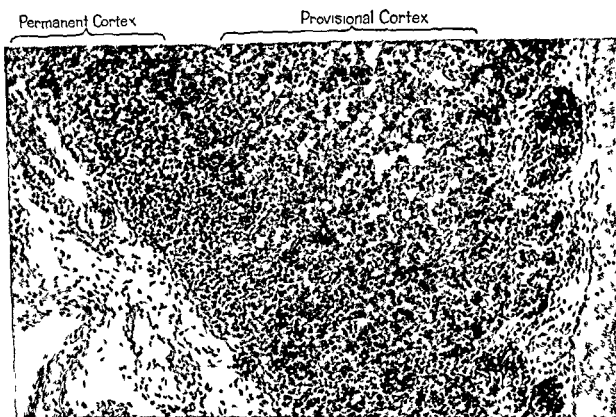


FIG 336 Photomicrograph ($\times 110$) of developing adrenal of a nine-week human embryo. Location of section is shown by rectangle in Fig 335. Med, clusters of chromaffin cells becoming embedded in the cortex to form primordium of medulla.

rapidity following birth, a degeneration of the provisional cortex occurs. This greatly reduces it by the end of the first postnatal month, and leaves little if any trace of it by the end of the first year. As the provisional cortex undergoes involution, the permanent cortex begins to differentiate, but it does not at first keep pace with the rate of regression of the provisional cortex and there is, in consequence, an actual postnatal drop in the total weight of the adrenal (Fig 113). According to Maximow, the full histological differentiation of the cortex into the three zones characteristic of the adult is not completed until about the third year after birth, the innermost of these zones (zona reticularis) being the last to become established.

Abnormalities of Chromaffin System and Adrenal The most common developmental anomalies of the adrenal are related to its dual origin. Acces-

sory cortical or medullary masses may be found at a variety of levels along the mid-dorsal body-wall. As one would expect from the manner in which they develop, such accessory masses tend to lie along the course of the dorsal aorta and to remain retroperitoneal in position. Not infrequently, however, accessory cortical or medullary masses may become adherent to the connective tissue about the gonads while they still lie near their position of origin. When this occurs in a female, accessory adrenal tissue may be carried away from the body-wall out into the broad ligament. In a male, the departure from the place of origin is much more striking, for accessory adrenal tissue, either cortical or medullary, may be carried along by the testes in their descent into the scrotum. A mass of adrenal tissue thus associated with the gonads is sometimes called the *accessory adrenal of Marchand*. The very frequent occurrence of accessory adrenal tissue in irregular and often unsuspected places greatly complicates experimental work depending on complete removal of the adrenals.

Development of the Urogenital System

The urinary and reproductive systems are so closely related both anatomically and embryologically that they must inevitably be considered together. Neither system is particularly simple in organization and the two of them together present a formidable array of structures. Naturally the development of such a composite group involves much of special interest to the embryologist. We shall see organs formed by the secondary association of parts which arose independently at different places. Certain organs appear and then disappear completely without ever having become functional. Other organs fall into disuse in their original capacity and begin to degenerate only to have some part seized upon and salvaged by a new organ for a new function. We have, as it were, many characters in the story of the development of these systems, and each character, individually, is doing things of interest. Sooner or later their activities cross. The method of the novelist in dealing with such a situation would be to switch from one character to another to keep us in confusion and suspense as to what is going to happen next. Our method in dealing with this embryological story should be exactly the reverse. To prevent the various threads of the story from becoming entangled we must, as far as possible, follow one group of structures from their origin to their completion before becoming involved with another. Because the urinary system appears earlier than the reproductive system, we shall take it up first and follow it through. Then we must return to young embryos and pick up the story of the internal reproductive system, watching constantly its relations to that of the excretory system with which we have become familiar. Yet again we must go back and follow the differentiation of the external genitalia. This approach may appear circuitous, but any attempt to develop all the threads of the story synchronously would lead only to confusion.

URINARY SYSTEM

General Relationships of Pronephros, Mesonephros, and Metanephros. As a preface to the account of the development of the human urinary organs, it is desirable to review certain facts about the structure and development of the excretory organs in the vertebrates generally. Without such information as a background, the story of the early stages of the formation of these organs in any of the higher mammals seems utterly without logical sequence. With it, the progress of events encountered seems but natural, because it is so

clearly an abbreviated recapitulation of conditions which existed in the adult stages of ancestral forms

There occur in adult vertebrates three distinct excretory organs. The most primitive of these is the pronephros, which exists as a functional excretory organ only in some of the lowest fishes. As its name implies, the pronephros

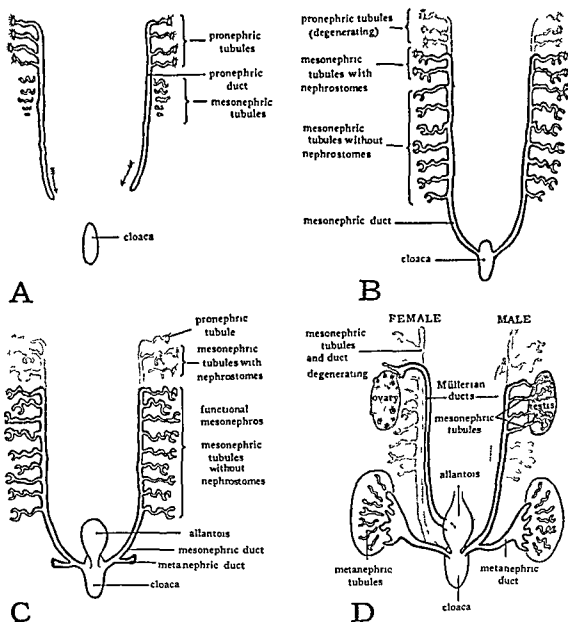


FIG. 337 Schematic diagrams to show relations of pronephros, mesonephros, and metanephros

is located far cephalically in the body. In all the higher fishes and in the amphibia the pronephros has degenerated and its functional rôle has been assumed by the mesonephros, a new organ located farther caudally in the body. In birds and mammals a third excretory organ develops caudal to the mesonephros. This is the metanephros, which constitutes our own permanent kidney. All three of these nephric organs are paired structures located retro-peritoneally in the dorsolateral body-wall. Each consists essentially of a group

of tubules which discharge by way of a common excretory duct. In the different nephroi the tubules vary in structural detail but their functional significance is, in all cases, much the same. They are concerned in collecting waste material from the capillary plexuses associated with them and passing it on to excretory ducts by way of which it is finally eliminated from the body.

In the embryological development of the mammalian urinary system, pronephros, mesonephros, and metanephros appear in succession, furnishing an excellent epitome of the same evolutionary history which may be learned in more detail from comparative anatomy. In embryos sufficiently young we find only a rudimentary pronephros. It consists of a group of tubules (Fig 337, A) emptying into ducts called the pronephric ducts, which extend caudad and ultimately come to discharge into the cloaca.

A little later in development there arises, in close proximity to each pronephric duct, a second group of tubules more caudal in position than the pronephric tubules. These are the mesonephric tubules. In their growth they extend toward the pronephric ducts and soon open into them (Fig 337, B). Meanwhile, the pronephric tubules begin to degenerate and the ducts which originally arose in connection with the pronephros are appropriated by the developing mesonephros. After the degeneration of the pronephric tubules, these same ducts lose their original name and are called mesonephric ducts because of their new associations (Fig 337, C).

At a considerably later stage outgrowths develop from the mesonephric ducts near their cloacal ends (Fig 337, C). These outgrowths form the ducts of the metanephroi. They grow dorsolaterad and eventually connect with a third group of tubules which constitute the metanephros (Fig 337, D). With the establishment of the metanephroi, or permanent kidneys, the mesonephroi begin to degenerate. The only parts of the mesonephric system to persist, except in vestigial form, are some of the ducts and tubules which, in the male, are appropriated by the testis as a duct system (Fig 337, D, right).

Pronephros In human embryos the pronephros is an exceedingly transitory structure. *Pronephric tubules* begin to appear in embryos of nine to ten somites (late in the third week). In all about seven pairs of tubules develop, opposite the seventh to the fourteenth somites. The most cephalic of these tubules, which are the first formed, are likely to show regressive changes before the last in the series appear late in the fourth week of development (23- to 25-somite embryos). Even at the height of their development the pronephric tubules of birds and mammals are vestigial structures that merely suggest in sketchy recapitulation the arrangement characteristic of the functional pronephric tubules of lower forms (Cf Fig 338, A, B).

The *pronephric duct* arises by the extension caudad of the distal end of each pronephric tubule until it meets and fuses with the tubule behind it to form a continuous channel. The duct thus established continues to grow caudad beyond the level of the tubules until it eventually opens into the cloaca (Fig 337). Since the pronephric tubules never become functional in mammalian embryos, we need give them no further consideration. The pronephric duct,

clearly an abbreviated recapitulation of conditions which existed in the adult stages of ancestral forms

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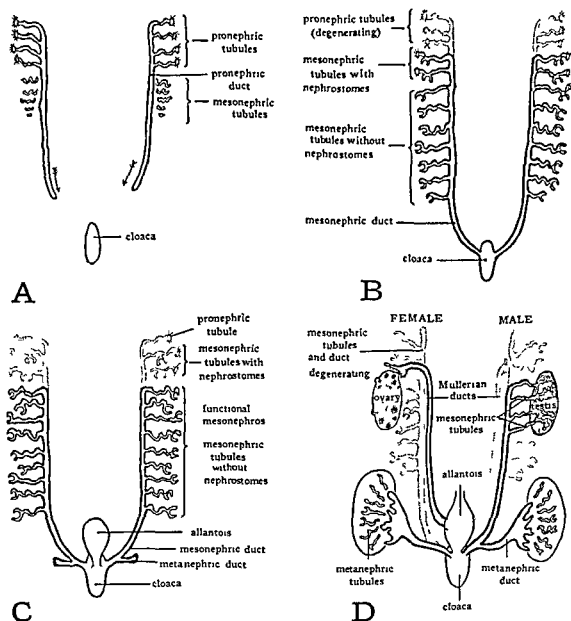


FIG 337 Schematic diagrams to show relations of pronephros, mesonephros, and metanephros

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middle of the fourth week of development (embryos of 18 to 20 somites) At first blind vesicles, the young tubules soon make connection with the pronephric duct With the degeneration of the pronephric tubules and its appropriation by mesonephric tubules, the pronephric (primary nephric) duct becomes known as the *mesonephric duct* The first mesonephric tubules usually appear at the level of the fourteenth somite Extension of tubule formation caudad from the point of its initiation is rapid, and by five weeks (7- to 8-mm embryos) has reached its most caudal extent at the level of the twenty-sixth somite (second lumbar segment) Early in the growth of the mesonephros a few tubules are formed cephalic to the fourteenth somite so that mesonephric tubules overlap, for a time, the more caudally located of the pronephric tubules This condition is, however, transitory and the more cephalic mesonephric tubules as well as the pronephric tubules soon disappear In bird embryos some of these most cephalically located mesonephric tubules show *rudimentary nephrostomes* reminiscent of those seen in the functional mesonephros of more primitive forms (Cf Fig 338, C, D) Most, if not all, of the tubules in the mammalian mesonephros slur over this interesting phase in recapitulation and develop without a nephrostome

With the progressive degeneration of the most cephalic tubules and the formation of new tubules from the intermediate mesoderm farther caudally, the mesonephros appears to move back in the body as development progresses As its cephalic end degenerates the shrunken tissues, together with the enveloping fold of splanchnic mesoderm, come to constitute the so-called *diaphragmatic ligament of the mesonephros* (Fig 358) As the process of tubule formation involves a given level, the nephrogenic tissue is soon completely converted into young tubules, two or more being formed opposite each somite With new tubule formation at caudal levels about keeping pace with tubule degeneration at the cephalic pole of the mesonephros, embryos of from four to nine weeks maintain a fairly constant number of tubules, there being about 30 to 34 on either side during this period

Considering now in more detail the process of the formation of individual tubules, we find when they are first budded off from the intermediate mesoderm that they appear as cell clusters very close to, but not in contact with, the mesonephric (old pronephric) duct (Fig 339, A) These primordial cell groups become elongated and one end of each growing cell cord soon fuses with the duct Once they have attained connection with the duct, the originally solid tubules become hollowed out and increase rapidly in length (Fig 339, B, C) Starting from a simple S-shaped configuration, their pattern is complicated by secondary bendings (Fig 339, D, E) This growth in length greatly increases their surface exposure, thereby enhancing their capacity for interchanging fluid and waste materials with the blood in the adjacent capillaries

RELATIONS OF MESONEPHRIC TUBULES TO VASCULAR SYSTEM The relations of the mesonephric tubules to the vascular system are indicated schematically in Fig 339, E, F The mesonephros is fed by many small arteries arising

however, becomes of importance through its subsequent relations to the mesonephros

Mesonephros The mesonephros in young mammalian embryos attains a considerable degree of development. Its tubules become highly differentiated and, pending the development of the metanephros, are believed to become active in the elimination of nitrogenous waste. As was the case with the

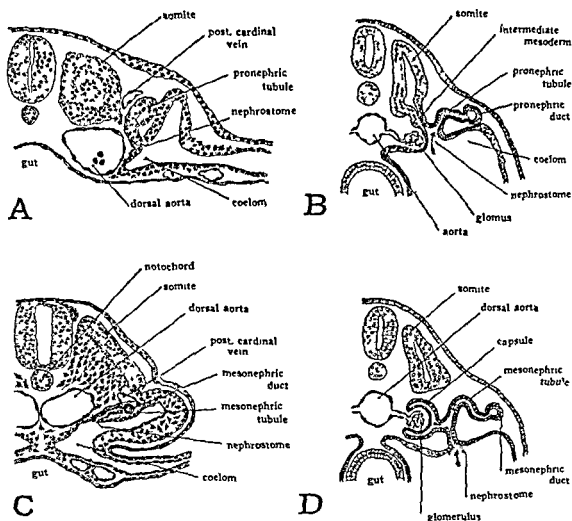


FIG 338 Drawings to show nephric tubules A, Drawing from transverse section through twelfth somite of 16-somite chick to show pronephric tubule (After Lillie) B, Schematic diagram of functional pronephric tubule (After Wiedersheim) C, Drawing from transverse section through seventeenth somite of 30-somite chick to show primitive mesonephric tubule D, Schematic diagram of functional mesonephric tubule of primitive type (After Wiedersheim)

pronephric tubules, the *mesonephric tubules* are derived from the intermediate mesoderm. At the time the tubules arise from it, the intermediate mesoderm shows no trace of segmentation. When viewed in reconstructions or dissections showing its longitudinal extent, it appears as a continuous band connecting the somites with the lateral mesoderm. For this reason the intermediate mesoderm is sometimes spoken of as the *nephrogenic cord*.

In human embryos mesonephric tubules begin to be formed during the

middle of the fourth week of development (embryos of 18 to 20 somites) At first blind vesicles, the young tubules soon make connection with the pronephric duct With the degeneration of the pronephric tubules and its appropriation by mesonephric tubules, the pronephric (primary nephric) duct becomes known as the *mesonephric duct* The first mesonephric tubules usually appear at the level of the fourteenth somite Extension of tubule formation caudad from the point of its initiation is rapid, and by five weeks (7- to 8-mm embryos) has reached its most caudal extent at the level of the twenty-sixth somite (second lumbar segment) Early in the growth of the mesonephros a few tubules are formed cephalic to the fourteenth somite so that mesonephric tubules overlap, for a time, the more caudally located of the pronephric tubules This condition is, however, transitory and the more cephalic mesonephric tubules as well as the pronephric tubules soon disappear In bird embryos some of these most cephalically located mesonephric tubules show *rudimentary nephrostomes* reminiscent of those seen in the functional mesonephros of more primitive forms (Cf Fig 338, C, D) Most, if not all, of the tubules in the mammalian mesonephros slur over this interesting phase in recapitulation and develop without a nephrostome

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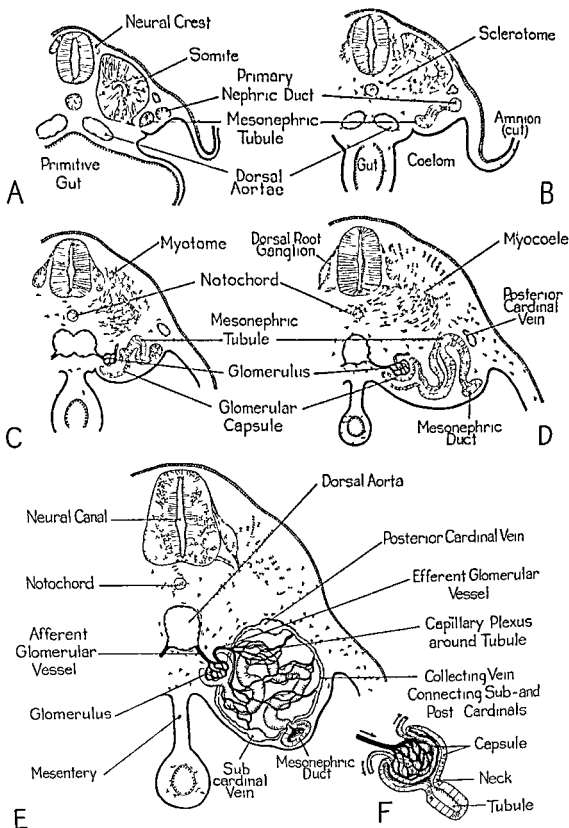


FIG 339 Development of mesonephric tubules and their vascular relations
 A, Tubule primordium still independent of duct B, Union of tubule with primary nephric duct C, Early stage in development of glomerulus and capsule D, Further development of capsule and lengthening of tubule E, Relations of blood vessels to well developed mesonephric tubule F, Glomerulus and capsule, enlarged

ventrolaterally from the aorta. Each of these arterial twigs pushes into the dilated free end of a developing tubule, forming from it a double-walled cup called a *glomerular (Bowman's) capsule* (Fig 339, D-F). Within the capsule the artery breaks up into a knot of capillaries known as the *glomerulus*. Blood from the glomerulus leaves the capsule over one or more vessels (efferent with reference to the glomerulus), which again break up into capillaries and form a plexus in close relation to the body of the tubule in its tortuous course from glomerulus to duct. From these capillaries the blood passes to collecting veins which are for the most part peripherally located in the mesonephros and more or less circularly disposed about it (Fig 339, E). These collecting veins form a freely anastomosing system connecting with both the posterior cardinals and the subcardinals, through which the blood is eventually returned to the general circulation.

METHOD OF FUNCTIONING OF NEPHRIC TUBULES The method of functioning of the nephric tubules is sufficiently interesting to warrant closer scrutiny. The pronephric tubules, the mesonephric tubules with nephrostomes, and the more highly specialized type of mammalian mesonephric tubules without nephrostomes all operate in the same basic manner although each has its own functional peculiarities. In the pronephric tubule (Fig 338, B) the fluid passing through the tubule to the excretory duct, and serving as a vehicle carrying waste materials, is drawn in from the coelom by way of a funnel-shaped opening (nephrostome) lined with cilia beating from the coelom toward the tubule. A ridge of highly vascular tissue (*the glomus*) bulges toward the nephrostome providing a mechanism whereby waste materials may diffuse from the vascular system into the fluid as it passes out the tubules. The primitive type of mesonephric tubule has a nephrostome similar to that of a pronephric tubule, but it has in addition a new mechanism in the form of an encapsulated tuft of capillaries, *the glomerulus* (Fig 338, D). This provides for the filtration of fluid from the blood stream through the thin capillary walls of the glomerulus and the thin inner wall of the capsule into the lumen of the tubule. In the characteristic mammalian type of mesonephric tubule (Fig 339) no nephrostome is formed and the tubule receives all its fluid by way of glomerular filtration. To speak figuratively, it is as if having experimented with the new glomerular mechanism Nature had decided that it would work and that the old nephrostome, for a time conservatively retained along with the glomerulus, could finally be completely abandoned. It is important to note that the capillaries after leaving the glomerulus form a plexus about the tubules before they enter the sub- or postcardinal veins (Fig 339, E). The brilliant experiments of Richards and his co-workers have made it evident that the action of the glomerulus is largely an unselective filtration that provides a liberal amount of fluid entering the tubule. While passing through the tubules this fluid is acted upon by the epithelial cells in the tubular walls. These cells selectively absorb certain chemical substances such as salts and sugars and return them to the blood in the efferent capillaries associated with this part of the tubule. Along with such substances a considerable amount of

water is also taken back into the blood passing through the efferent capillaries. Thus the nitrogenous and other waste materials which are the by-products of metabolism are concentrated and continue through the tubules to pass off by way of the ducts.

Although it is relatively more conspicuous earlier in development, the mesonephros does not attain its greatest actual bulk until well along toward the close of the second month of development. There is considerable difference among mammals as to the degree of development attained by the mesonephros. For example that of man, the cat, and the guinea pig remains relatively small. The rabbit and the pig, on the other hand, have a very large mesonephros. There is some reason to suspect that this difference in the size attained by the mesonephros is inversely related to the excretory efficiency of the placenta characteristic of the different species. Regardless of the extent of its early development, when the metanephros is well established the mesonephros undergoes rapid involution and ceases to be of importance in its original capacity. In dealing with the reproductive system, however, we shall see that its ducts and some of its tubules still persist and give rise to structures of vital functional importance.

Establishing of the Metanephros or Permanent Kidney The metanephros has a dual origin. It arises in part from tissue budded off from the mesonephric duct, and in part from intermediate mesoderm situated caudal to the level of the mesonephros. Of these two separate primordia, the one derived from the mesonephric duct is the first to appear. In embryos as small as 5 or 6 mm. this *metanephric diverticulum*, as it is called, can be identified as a tiny budlike outgrowth just cephalic to the point where the mesonephric duct opens into the cloaca (Fig. 340, A). Almost from its first appearance the blind end of the metanephric diverticulum is dilated, foreshadowing its subsequent enlargement to form the *pelvis of the kidney*. The portion of the diverticulum near the mesonephric duct remains slender, presaging its eventual conversion into the *ureter* (Fig. 341).

As the metanephric diverticulum pushes out, it collects about its distal end mesoderm from the nephrogenic cord caudal to the level at which mesonephric tubules were formed. The original relations of this mass of mesoderm are soon entirely lost because it closely invests the pelvic end of the metanephric diverticulum and is pushed farther and farther away from its point of origin as the diverticulum continues to grow cephalad (Figs. 340, 349). This mesoderm is destined to give rise to the secretory tubules of the metanephros, or permanent kidney, and is consequently termed *metanephrogenic tissue*. Its change in relations should not lead to overlooking the fact that it is intermediate mesoderm like that giving rise to pro- and mesonephric tubules, only from a more caudal level in the body. (The metanephric diverticulum arises at the level of the twenty-eighth somite. This is the segment that becomes the fourth lumbar. See Fig. 182.)

While the metanephric primordium is migrating cephalad, it increases rapidly in size and encroaches on the space occupied by the mesonephros.

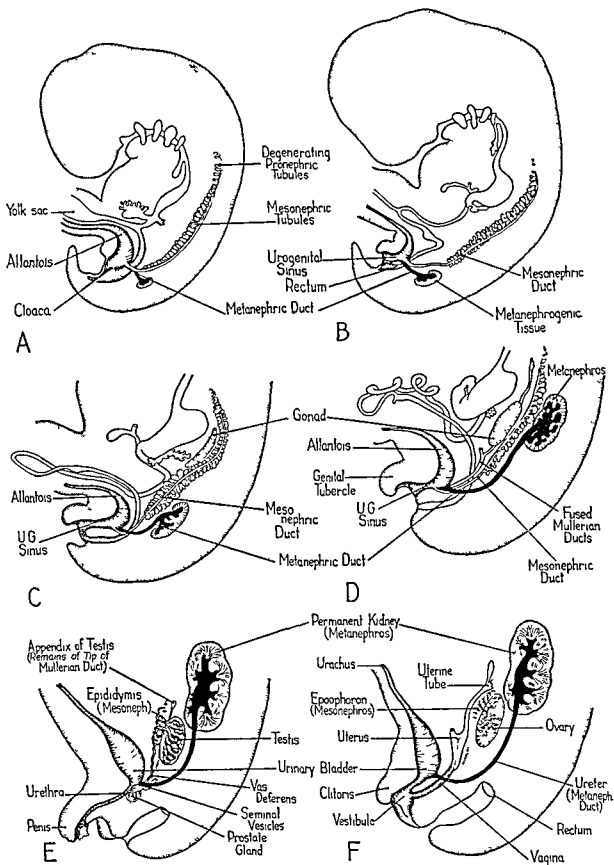


FIG. 340 Diagrams showing relative sizes and positions of nephric organs of human embryo at various stages of development A, Early in fifth week (Adapted from several sources covering 5- to 6-mm embryos) B, Early in sixth week (Modified from Shukinami's 8-mm embryo) C, Seventh week (Modified from Shukinami's 14 6-mm embryo) D, Eighth week (Adapted from Shukinami's 23-mm embryo and the Kelly and Burnam 25-mm stage) E, Male at about three months—schematized F, Female at about three months—schematized

Coincidentally, rapid internal differentiation is progressing. The pelvic end of the diverticulum expands within its investing mass of metanephrogenic mesoderm and forms extensions cephalad and caudad which are called the *major calyces* (Fig 341, D). These soon show subdivisions which are known as the *minor calyces* (Fig 341, E). With the formation of the calyces the shape of the pelvic cavity and its extensions is brought into a configuration much like that of the adult.

Meanwhile, from the tip of each minor calyx there arise numerous outgrowths which push radially into the surrounding mass of nephrogenic mesoderm. These outgrowths become hollow, forming the primary *straight collecting*

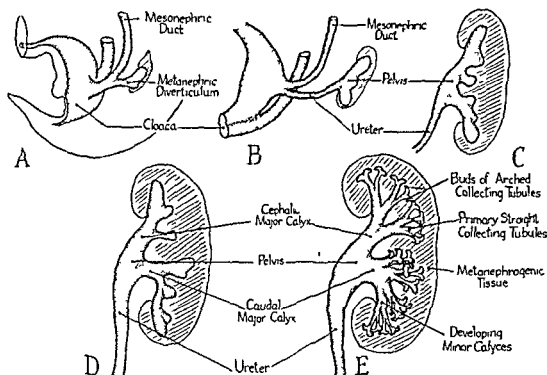


FIG 341 Diagrams showing growth and differentiation of metanephric diverticulum A, At 4 mm B, At 8 mm C, At 11 mm D, At 13 mm E, At 20 mm

tubules of the kidney (Fig 341, E, 342, A). The group of straight collecting tubules associated with a minor calyx are the drainage channels for a natural unit of kidney structure. They, together with the tubules that develop from the immediately surrounding metanephrogenous mesoderm, constitute a *renal lobe* (Figs 342 D, 347).

The first changes in the metanephrogenous mesoderm which presage the formation of the uriniferous tubules occur near the growing ends of the terminal branches of the system of straight collecting tubules. The mesodermal cells become arranged in small vesicular masses which lie adjacent to the blind end (ampulla) of a collecting tubule (Fig 343, A). Each of these vesicular cell masses is destined to become a *uriniferous tubule* draining into the straight collecting tubule adjacent to which it arises. As the developing tubules extend toward the end of the collecting duct, the duct itself branches out to meet

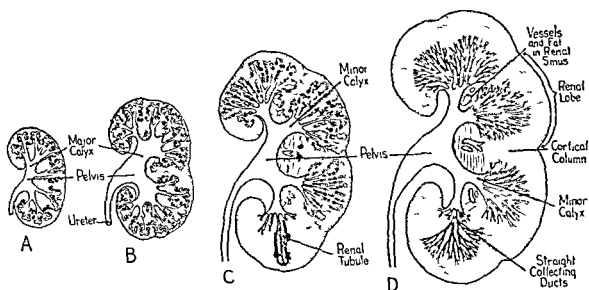


FIG 342 Diagrams showing succession of branches derived from primary straight collecting tubules (Redrawn, with some modification, after Kelly and Burnam "Diseases of Kidneys, Ureters, and Bladder," courtesy, D Appleton-Century Co) Note the way in which a group of the branches of the primary straight collecting ducts ultimately form the drainage system for a renal lobe

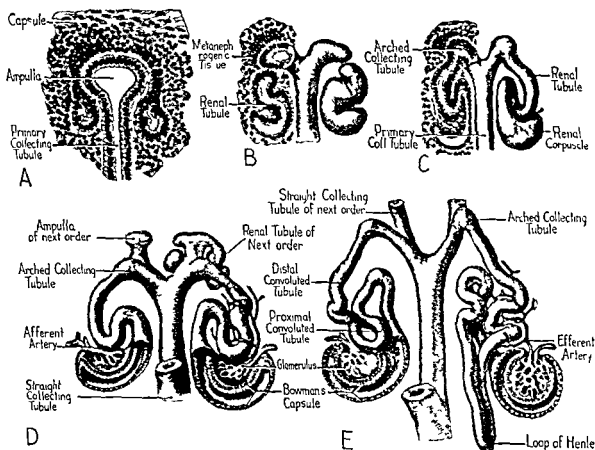


FIG 343 Drawings showing a series of stages in development of metanephric tubules (After Huber, from Kelly and Burnam "Diseases of Kidneys, Ureters, and Bladder," courtesy, D Appleton-Century Co)

them (Fig 343, B) and soon the two become confluent. In Fig 343, C this condition at a slightly more advanced stage is represented schematically. The drawing shows only two uriniferous tubules in relation to the end of the collecting duct, whereas there are actually more—usually four—forming a radiating crown of metanephric (uriniferous) tubules about the tip of the straight collecting tubule (Fig 344). In this stage the young metanephric tubules are very similar to mesonephric tubules (cf Fig 339), but in their later development they become much more elaborately convoluted and the configuration they assume is highly characteristic.

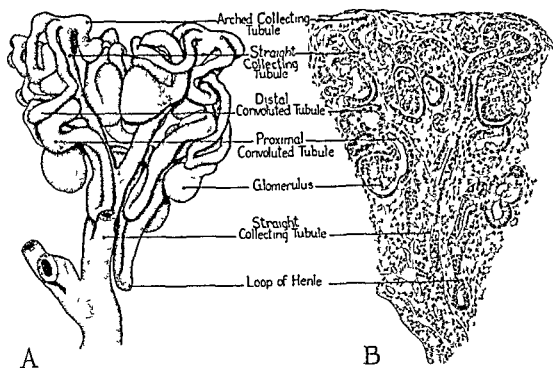


FIG 344 Collecting and uriniferous tubules of kidney of a human embryo of 11 weeks (C-R, 65 mm) (Redrawn from Huber, *Am J Anat*, Vol 4, Suppl, 1905) A, Model of a primary collecting tubule, starting just proximal to its origin from the pelvis of the kidney. Of the four second-order branches, three are represented as cut off and only one is modeled to show the two collecting tubules of the third order which arise from it, and their associated uriniferous tubules. B, Section ($\times 85$) typical of those used in constructing model shown in A.

TYPICAL PLAN OF A FULLY DEVELOPED METANEPHRIC TUBULE Shown in Fig 345, C is a typical plan of a fully developed metanephric tubule. Considering its parts in the order in which the fluid traverses them, the first is the *renal corpuscle*, consisting of a glomerulus enclosed in a capsule (Bowman's capsule) quite similar structurally and functionally to the corresponding parts in a mesonephric tubule (cf Figs 339, F 345, B). Beyond the renal corpuscle is a very tortuous stretch of uriniferous tubule known as the *proximal convoluted tubule*. Beyond its proximal convoluted portion the tubule is continued into a long loop with relatively straight limbs—the *loop of Henle* (Fig 345, C). The loops of Henle are so placed that they extend from the outer part (cortex) of the kidney into the medullary portion of the kidney adjacent to the calyces.

The closed part of the loop thus lies "deep" in a renal lobe and, accordingly the limb of the loop which extends from the proximal convoluted tubule toward the closed part of the loop is known as the descending limb, while that returning again toward the cortex is known as its ascending limb. The ascending limb gives over into a second tortuous portion known as the *distal convoluted tubule* (Fig. 345, C). Beyond its distal convoluted portion the tubule swings in a gentle curve toward the straight collecting tubule into which it

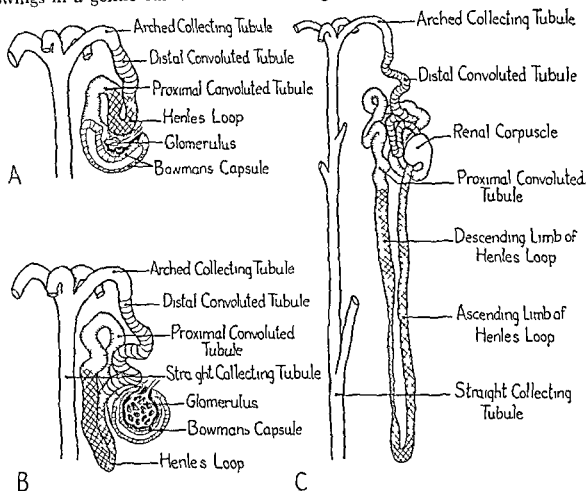


FIG. 345 Renal tubules at different stages of development schematically shaded to indicate corresponding regions (Redrawn from Prentiss, after Huber and Stoerk.)

discharges. This curved portion is the *arched collecting tubule*. As can be seen by studying the series of developmental stages shown in Fig. 343, it is in this region that the union was originally made between the primordial straight collecting tubules derived from the metanephric diverticulum, and the uriniferous tubules derived from the metanephrogenic mesoderm.

Growth of the Kidney A careful study of Figs. 343-345 will give a good review of the main developmental steps involved in the differentiation of individual uriniferous tubules. An additional word of explanation is, however, necessary to indicate the manner in which the duct and tubule systems of the metanephros are expanded so they can keep pace functionally with the mass of the growing body for which they must effectively carry on excretion. Reference has already been made to the way in which the straight collecting tubules

of the developing kidney branch and rebranch until the group of them entering a minor calyx fan out to form the drainage system for all the uriniferous tubules in a renal lobe (Fig 342) As each generation of straight collecting tubules is formed, new uriniferous tubules develop about their tips as indicated in Fig 343, A-C Further growth is at the same time provided for by the budding off of new orders of straight collecting tubules from about the point where the uriniferous, and the already established straight collecting tubules joined (See "Ampulla of next order," Fig 343, D) Stated more fully, this



FIG 346 Photomicrograph ($\times 50$) of developing metanephros at three months (C-R, 65 mm)

label designates the bud from which the next order of straight collecting tubules will arise by the lengthening of its basal portion, and into which the next order of uriniferous tubules will empty, distally) Each time new straight collecting tubules develop, new uriniferous tubules are formed at their growing tips in a manner precisely similar to that shown for the previous generation of tubules (Fig 343, A-C)

In the growth of the kidney, the straight collecting tubules continue thus to form new orders of branches By the end of the fifth fetal month some 10 to 12 generations of them have been formed Meanwhile, the pelvis and calyces have been expanding until the first four orders of straight collecting tubules

are resorbed. Thus in the fully formed kidney the 16 to 20 large straight tubules (papillary ducts) that open into a minor calyx at the apex of a renal lobe represent the fifth order of straight collecting tubules. The tubules formed

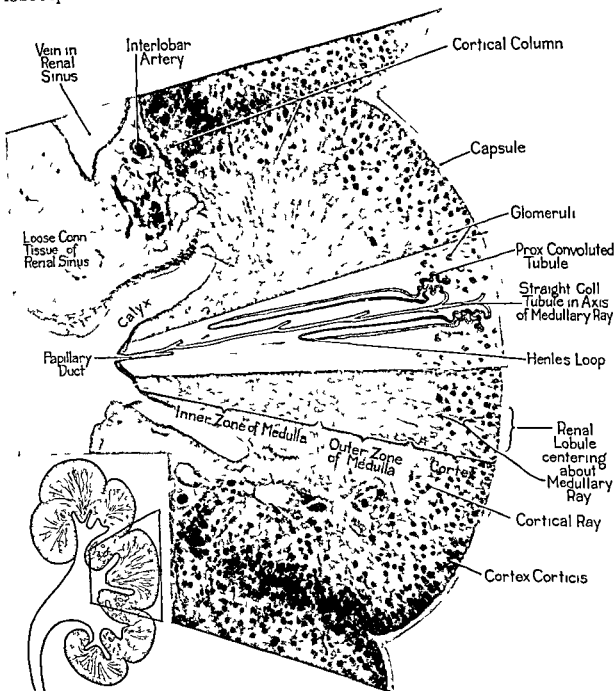


FIG 347 Photomicrograph (×18) of one lobe of the metanephros of a human embryo at the beginning of the sixth month (C-R, 200 mm) Inset, lower left, shows the part of the kidney appearing in the photograph. A schematic diagram of the arrangement of the renal tubules about a straight collecting tubule has been cut into the center of the lobe. This diagram represents the structures of a renal lobule spread out for the sake of clearness.

by the higher orders of branches elongate to form the many smaller straight collecting tubules extending from the medulla into the radiate zone of the cortex (Fig 347).

It is implied by what has already been said about the way uriniferous

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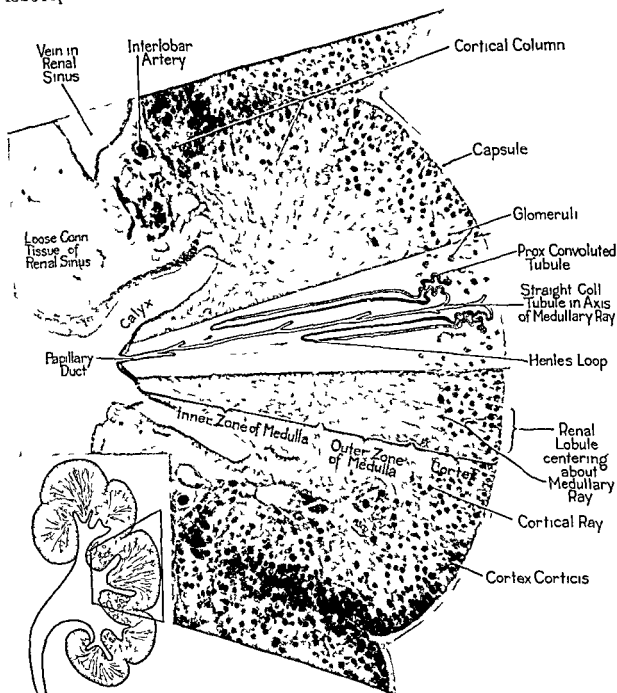


FIG 347 Photomicrograph ($\times 18$) of one lobe of the metanephros of a human embryo at the beginning of the sixth month (C-R, 200 mm). Inset, lower left, shows the part of the kidney appearing in the photograph. A schematic diagram of the arrangement of the renal tubules about a straight collecting tubule has been cut into the center of the lobe. This diagram represents the structures of a renal lobule spread out for the sake of clearness.

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tubules are formed at the tips of the successive generations of collecting tubules that the tubules also increase in numbers by the formation of new generations added peripherally. Careful estimates indicate that by the time of birth some 12 to 14 generations of tubules have been thus formed and that, in spite of the degeneration of many of the tubules belonging to the earlier generations each kidney has approximately a million uriniferous tubules. Some additional generations of tubules may be formed during the first months after birth but the greater part of the postnatal increase in the size of the kidney appears to be due to the growth of the tubules rather than to further increase in their numbers. A good conception of the rapid increase in the number of tubules taking place during the growth of the kidney can be gleaned by comparing the small number of glomeruli seen in the cortex of the kidney at three months

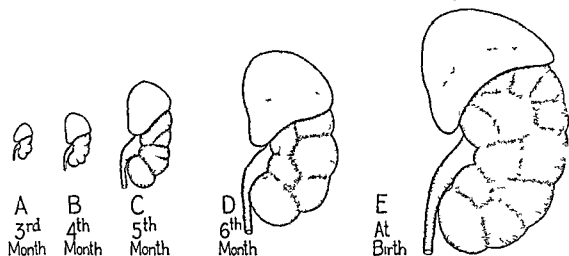


FIG. 348 Drawings showing actual size of kidney and of adrenal gland at various stages of development

(Fig. 346) with the greatly augmented numbers in the cortex of a six-month kidney (Fig. 347). The increase in the total bulk of the kidney is best shown by drawings to actual size such as the series shown in Fig. 348.

Relations of Blood Vessels to Kidney Tubules The blood supply to the metanephros, instead of coming directly from the aorta by numerous small branches as is the case in the mesonephros, is brought in from the aorta through the renal artery and its branches. Nevertheless, the relations of the smaller vessels to the tubules are essentially similar in the two organs. In each, an arterial twig breaks up into a glomerulus within a capsule at the distal end of the excretory tubule. Likewise, in each, an efferent vessel leaves the glomerulus to break up in a meshwork of capillaries in close relation to the rest of the tubule. Functionally, too, the metanephric tubule works in a manner similar to that already described for the mesonephric tubule. The renal corpuscle is essentially a filtration mechanism which passes a large amount of fluid from the blood stream into the distal end of the uriniferous tubule. The fact that the branches to the glomeruli are fed by generous-sized arteries direct from the aorta permits them to operate under a relatively high pulse pressure which undoubtedly increases the efficiency of this filtration process. The

capillaries carrying the blood away from the glomerulus are under much less pressure where they come into relation with the various parts of the tubule. Although the experimental evidence is still fragmentary as to details it seems clear that the epithelium of the convoluted tubules extracts and returns to the blood in these capillaries certain of the so-called threshold substances such as salts and sugars which are thus maintained at surprisingly constant levels of concentration. At the same time much of the water that entered the tubule in the renal corpuscle is taken back into the blood, thereby concentrating the urine before it passes out of the tubules into the straight collecting tubules.

Later Positional Changes of the Kidney When the metanephroi are first established they are located far caudally in the growing body (Fig 340, A, B), but as development progresses they come to lie relatively much further cephalad (Fig 340, C-F). Their own actual movement headward is not quite so great as their change in position at first glance would indicate. Part of their apparent migration is due to the rapid expansion of the portion of the body caudal to them. This rapid growth of the caudal part of the body, it will be recalled, was responsible also for the way the end of the slowly growing spinal cord comes to lie well up in the spinal canal, with the segmental nerves pulled downward to form the cauda equina (Fig 202). It is so much easier to describe the changing relations of the kidney as if they were entirely accounted for by its own migration that this factor of differential growth in the caudal region is frequently ignored. Recognition of the importance of differential growth in the process makes the changes in the relative position of the kidney no less striking. It will be recalled that the metanephric diverticulum arose opposite the twenty-eighth somite (fourth lumbar segment). Scrutiny of Fig 365, in which the segmental levels are indicated on the vertebrae, will show that toward the close of the third month the center of the kidney lies about opposite the second or third lumbar vertebra. At term (Fig 366), it has moved up opposite the first lumbar or even as high as the twelfth thoracic vertebra. There is, of course, as in all such processes considerable individual variability within normal limits.

More striking than the change in segmental level is the shift of the kidneys out of the pelvic part of the coelom. In young embryos the kidneys lie retroperitoneally, bulging into the narrow pelvic cavity caudal to the bifurcation of the aorta where it gives rise to the umbilical arteries. During the seventh week (Fig 349, A, B) the kidneys start to slide forward over the ridges formed by the umbilical arteries. By the ninth week they have cleared this narrowed portion of the coelomic chamber and come to lie against the dorsolateral body-walls above the arterial fork (Figs 349, C, D, 364). In this part of their ascent they are rotated about a quarter turn so that their convex borders, originally directed dorsally, become directed laterally. After this their changes in position are slower. They move cephalad about two more segments (cf Figs 365, 366) and settle more deeply into the subperitoneal fat and connective tissue on the inner side of the dorsal body-wall (Fig 349, D), gradually reaching their characteristic adult position (Fig 349, E).

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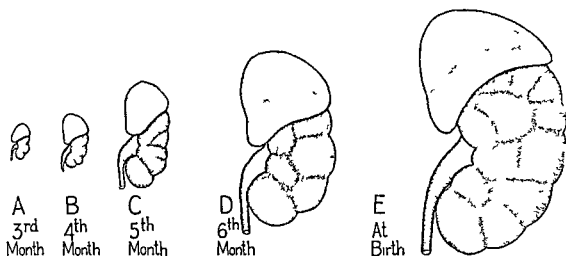


FIG. 348. Drawings showing actual size of kidney and of adrenal gland at various stages of development.

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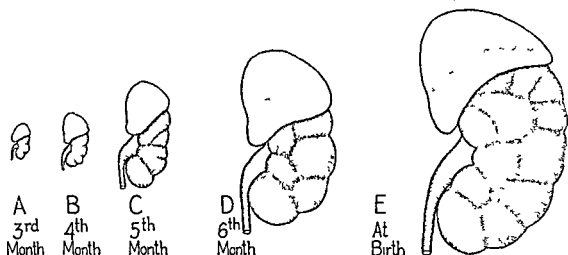


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Developmental Abnormalities of the Kidneys As might be expected from their embryological history, developmental defects of the kidney may be of a number of quite different types. Very rarely a kidney may entirely fail to develop (*agenesis*). Less uncommon than such complete *agenesis* is the *stunting* of a kidney on one side or the other (Fig. 350, D)

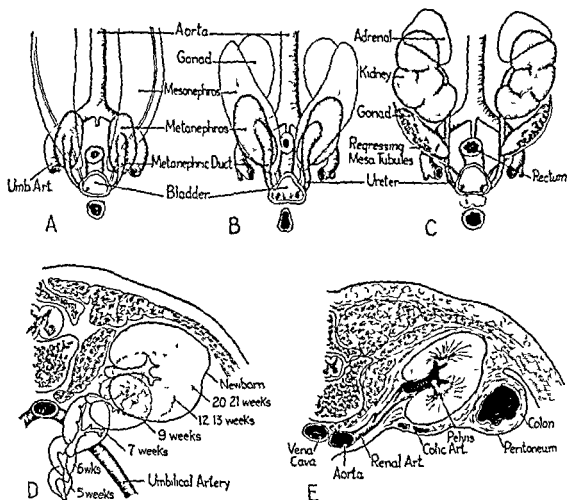


FIG. 349 Diagrams showing changes in position of kidney during development (Redrawn from Kelly and Burnam "Diseases of Kidneys, Ureters, and Bladder," courtesy, D. Appleton-Century Co.) A-C, Frontal views showing ascent of kidneys out of pelvis. Note their rotation, occurring chiefly as they rise above the common iliac arteries. D, Schematic composite diagram showing rotation of kidney as seen in a cross section of the body. E, Location of kidney as seen in a cross-section of the adult body at lumbar level.

There is a whole group of *abnormalities of position* which result from disturbances in the migration of the kidney. One of the kidneys may fail to ascend over the common iliac artery and remain lodged in the pelvis (Fig. 350, A). In the early part of their development, possibly as the two kidneys are crowded close together in passing the arterial fork, they may become fused to each other and so remain as they continue their ascent. Because of the resultant characteristic shape, such a condition is known as a "*horseshoe kidney*" (Fig. 350, B).

Very rarely indeed in their ascent both kidneys may be thrown over to the same side of the mid-line and fuse to form a large, irregular, unilateral

renal mass (Fig 350, C) Obviously abnormal conditions of the foregoing types are of serious functional import in proportion to the amount by which normal kidney tissue is reduced, or the blood supply to the dystopic kidney is disturbed All of them are of clinical interest because of the complications their presence may introduce into problems in physical diagnosis When surgery of

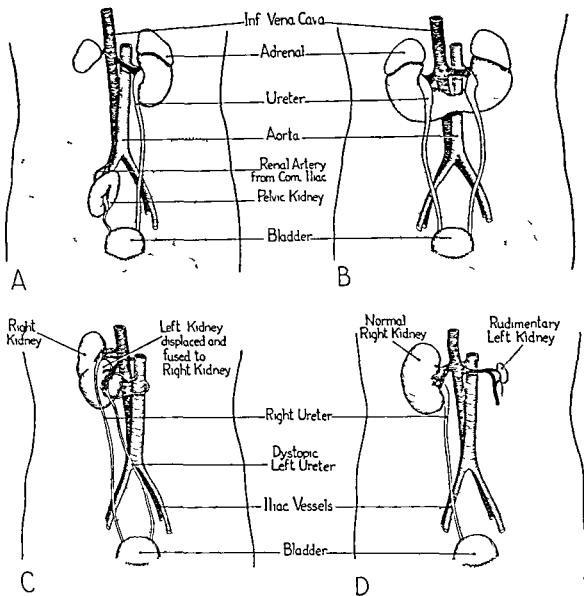


FIG 350 Four types of developmental disturbances of kidneys, sketched from museum preparations A, C, and D in the University of Michigan Anatomical Coll., B in the Dupuytren Museum, Paris A, Unilateral pelvic kidney B, Horseshoe kidney C, Dystopic left kidney fused to right kidney D, Nearly complete agenesis of left kidney

the region involved must be undertaken, the importance of a knowledge of the developmental disturbances which may be encountered is too self-evident to call for comment

A curious anomaly of rather surprising frequency is the formation of a *double ureter* on one or both sides When this occurs there is a tendency for the associated nephrogenic mass to be divided so part of it goes with the pelvic end of each ureter, giving the appearance of a double kidney (Fig 351) It would

be more accurate to speak of such cases as having a divided kidney because the two masses of renal tissue have, between them, a number of lobes equivalent to the normal number for a single kidney. Another peculiarity of the condition is the fact that the two ureters almost always cross each other as they ascend. A plausible embryological explanation for the constancy of this crossing is given in the hypothetical stages depicted in Fig. 352, after Kelly and Burnam. In the early stages it is assumed that the two ureters were uncrossed (Fig. 352, A, B). The crossing is supposed to be initiated because the more caudal of the two ureters (c) comes to open independently into the cloaca somewhat sooner than does the cephalic member of the pair. Thus, for a time, the originally more

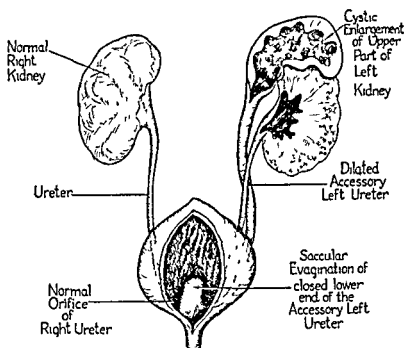


FIG. 351 Case of double left ureter and divided kidney in an infant (Sketched from autopsy 176,556, Path Anat Inst, Vienna)

cephalically located ureter (b) has its bladder end anchored to the mesonephric duct and is held back, while the bladder end of the other ureter (c) is free to slip cephalad past the opening of the mesonephric duct, as the kidney tissue with which it is associated moves cephalad. Whether it is substantiated by future work or not, this perhaps oversimplified explanation of the way double ureters come to be crossed is sufficiently logical to help one remember both the embryological processes involved and the peculiar complex of conditions presented by this anomaly.

A renal anomaly of very serious import results sometimes when there is failure to establish proper union between the straight collecting tubules and the independently arising uriniferous tubules (See Fig. 343, A, B). Under such circumstances the blind tubules continue to develop, forming glomeruli which even begin to function. Accumulation of urine within such tubules soon converts them into tense, fluid-filled vesicles. The internal pressure causes the epi-

thelial cells to thin out and degenerate, and at the same time causes hypertrophy of the surrounding connective tissue. Each blind tubule thus becomes a fluid-filled cyst. If the process occurs in large numbers of tubules, even the intervening uninvolved tubules are so compressed between adjacent cysts that they can not develop or function normally. The condition is known as *congenital polycystic kidney*. If the kidneys are extensively involved, such a condition is incompatible with postnatal survival when the placenta can no longer carry on the major part of the excretory functions for the growing individual.

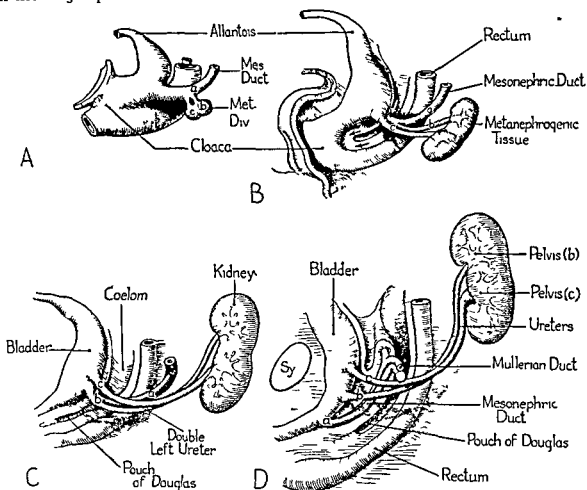


FIG 352 Schematic diagrams showing probable nature of the critical developmental steps involved in formation of double ureters (Redrawn from Kelly and Burnam "Diseases of the Kidneys, Ureters, and Bladder," courtesy, D Appleton-Century Co.)

Formation of Bladder and Early Changes in Cloacal Region In dealing with the development of the extra-embryonic membranes, we have already taken up the formation of the allantois as an evagination from the primitive hindgut (Figs 70, 78). Shortly after this occurs, the gut caudal to the point of origin of the allantois becomes enlarged to form the cloaca. When the cloacal dilation first appears, the hindgut still ends blindly, but there is an ectodermal depression under the root of the tail which sinks in toward the gut until the tissue separating the gut from the outside is very thin (Fig 353). This ectodermal depression is known as the *proctodaeum* and the thin plate of tissue still closing the hindgut is called the cloacal membrane. Eventually the

be more accurate to speak of such cases as having a divided kidney because the two masses of renal tissue have, between them, a number of lobes equivalent to the normal number for a single kidney. Another peculiarity of the condition is the fact that the two ureters almost always cross each other as they ascend. A plausible embryological explanation for the constancy of this crossing is given in the hypothetical stages depicted in Fig 352, after Kelly and Burnam. In the early stages it is assumed that the two ureters were uncrossed (Fig 352, A, B). The crossing is supposed to be initiated because the more caudal of the two ureters (c) comes to open independently into the cloaca somewhat sooner than does the cephalic member of the pair. Thus, for a time, the originally more

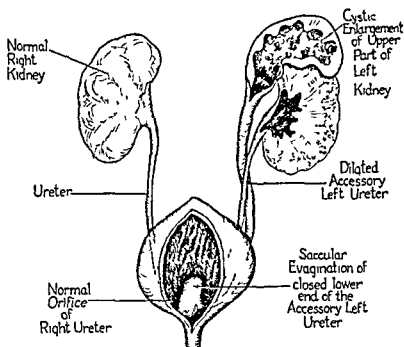


FIG 351 Case of double left ureter and divided kidney in an infant (Sketched from autopsy 176,556, Path Anat Inst, Vienna)

cephalically located ureter (b) has its bladder end anchored to the mesonephric duct and is held back, while the bladder end of the other ureter (c) is free to slip cephalad past the opening of the mesonephric duct, as the kidney tissue with which it is associated moves cephalad. Whether it is substantiated by future work or not, this perhaps oversimplified explanation of the way double ureters come to be crossed is sufficiently logical to help one remember both the embryological processes involved and the peculiar complex of conditions presented by this anomaly.

A renal anomaly of very serious import results sometimes when there is failure to establish proper union between the straight collecting tubules and the independently arising uriniferous tubules (See Fig 343, A, B). Under such circumstances the blind tubules continue to develop, forming glomeruli which even begin to function. Accumulation of urine within such tubules soon converts them into tense, fluid-filled vesicles. The internal pressure causes the epi-

353-355) The point of entrance of the mesonephric ducts, however, affords a landmark which is sufficiently accurate for all practical purposes. Before the urorectal fold has changed the relations, the mesonephric ducts open from either side into the cephalic part of the cloaca (Fig 353). After the urorectal fold has divided the cloaca, the mesonephric ducts appear to empty into the allantois (Fig 354). This gives us our bearings, for the mesonephric ducts are actually opening into the newly established urogenital sinus which is continuous with the allantois. Meanwhile, the proximal part of the augmented

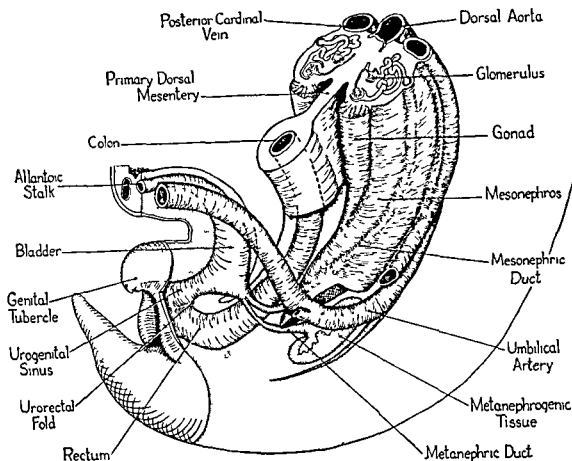


FIG 354 Schematic ventrolateral view of urogenital system of human embryo of 12 to 14 mm (about six weeks) (Redrawn from Kelly and Burnam "Diseases of Kidneys, Ureters, and Bladder," courtesy, D Appleton-Century Co.)

allantois has become greatly dilated and may now quite properly be called the *urinary bladder*. We should remember, however, that a considerable portion of the bladder has been formed from tissue which was originally part of the cloaca. During the third month the splanchnic mesoderm of the bladder wall begins to be differentiated into interlacing bands of smooth muscle and an outer covering of fibrous connective tissue. By the fourth month the layers characteristic of the adult organ are clearly recognizable.

Toward the umbilicus the allantoic stalk becomes reduced to form the *urachus* (Cf Fig 354 with 364, 365). In the latter part of fetal life the urachal lumen ordinarily closes, leaving an epitheloid cord surrounded by dense fibrous tissue extending from the apex of the bladder to the umbilicus. Post-

cloacal membrane ruptures, establishing a caudal outlet to the gut. This rupture is similar to the rupture of the oral plate which at an earlier stage of development establishes communication between the stomodaeum and the cephalic end of the primitive gut.

While the cloaca is thus acquiring an external outlet, important changes are taking place internally. The cloaca begins to be divided into two parts, a dorsal part which forms the rectum and a ventral part known as the *urogenital sinus*. This division is effected by the growth of the *urorectal fold*, a crescentic

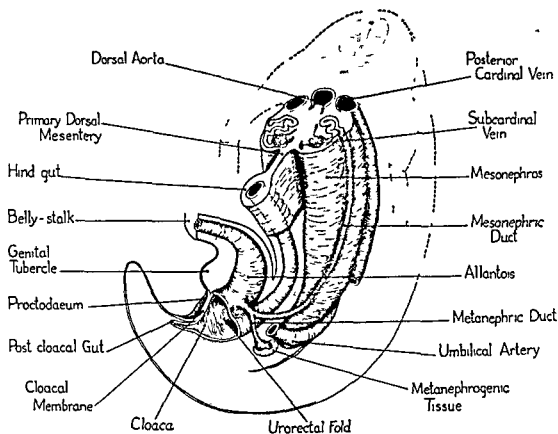


FIG. 353 Schematic ventrolateral view of urogenital system of human embryo between 4 and 6 mm (fifth week) (Redrawn from Kelly and Burnam "Diseases of Kidneys, Ureters, and Bladder," courtesy, D. Appleton-Century Co.)

fold which cuts into the cephalic part of the cloaca where the allantois and the gut meet and grows thence caudad toward the cloacal membranes. The two limbs of the fold bulge into the lumen of the cloaca from either side (Fig. 353). As the fold cuts progressively deeper into the cloaca, a wedge-shaped mass of mesenchyme follows into the epithelial fold, thus forming a robust septum between the urogenital sinus and the rectum (Fig. 354). The separation of the cloaca is complete before the cloacal membrane ruptures and its two parts, therefore, open independently (Fig. 355). The opening of the rectum is the anus, and that of the urogenital sinus is the ostium urogenitale.

The progress of the urorectal fold toward the cloacal membrane makes it difficult to keep track of the original limits of the allantois since as the urogenital sinus is lengthened it is, in effect, added on to the allantois (Cf Figs

353-355) The point of entrance of the mesonephric ducts, however, affords a landmark which is sufficiently accurate for all practical purposes. Before the urorectal fold has changed the relations, the mesonephric ducts open from either side into the cephalic part of the cloaca (Fig 353). After the urorectal fold has divided the cloaca, the mesonephric ducts appear to empty into the allantois (Fig 354). This gives us our bearings, for the mesonephric ducts are actually opening into the newly established urogenital sinus which is continuous with the allantois. Meanwhile, the proximal part of the augmented

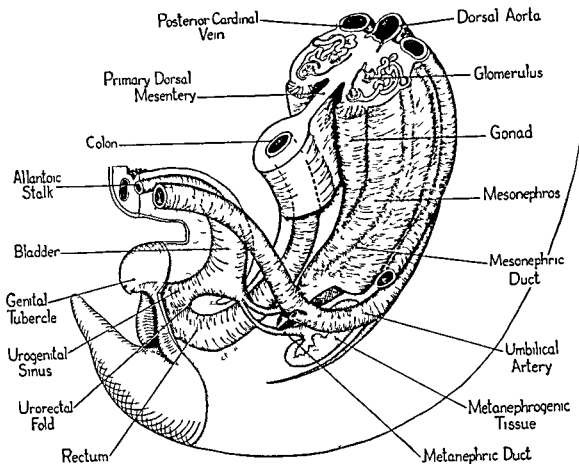


FIG 354 Schematic ventrolateral view of urogenital system of human embryo of 12 to 14 mm (about six weeks) (Redrawn from Kelly and Burnam "Diseases of Kidneys, Ureters, and Bladder," courtesy, D Appleton-Century Co)

allantois has become greatly dilated and may now quite properly be called the *urinary bladder*. We should remember, however, that a considerable portion of the bladder has been formed from tissue which was originally part of the cloaca. During the third month the splanchnic mesoderm of the bladder wall begins to be differentiated into interlacing bands of smooth muscle and an outer covering of fibrous connective tissue. By the fourth month the layers characteristic of the adult organ are clearly recognizable.

Toward the umbilicus the allantoic stalk becomes reduced to form the *urachus* (Cf Fig 354 with 364, 365). In the latter part of fetal life the urachal lumen ordinarily closes, leaving an epithelioid cord surrounded by dense fibrous tissue extending from the apex of the bladder to the umbilicus. Post-

nately the urachus is lengthened as the fundus of the bladder descends, and it is then known as the *middle umbilical ligament* (The paired lateral umbilical ligaments are formed from the postnatally closed portions of the umbilical, or allantoic, arteries)

In the growth of the bladder the terminal portion of the mesonephric duct is absorbed into the bladder wall. This absorption progresses until the mesonephric duct caudal to the point of origin of the metanephric diverticulum has disappeared. The end-result of this process is that the mesonephric and metanephric ducts open independently into the urogenital sinus. The metanephric

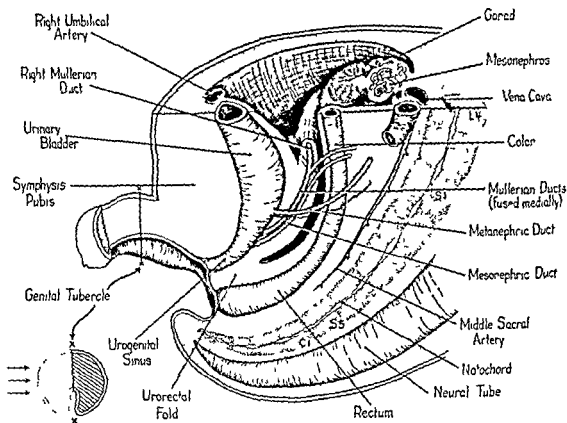


FIG. 355 Semischematic drawing of reconstruction of urogenital system of a human embryo of eighth week. (Modified from Keibel.)

duct, possibly due to traction exerted by the kidney in its migration headward, acquires its definitive opening somewhat lateral and cephalic to that of the mesonephric duct. It then discharges into the part of the urogenital sinus which was incorporated into the bladder. The mesonephric ducts open into the part of the urogenital sinus which remains narrower and gives rise to the urethra (cf Figs 353, 355). The urethra acquires different relations in the two sexes and the associated glands, also, are quite different in the male and in the female. It is, therefore, desirable to defer consideration of these structures and take them up in connection with the development of the external genitalia.

Developmental Abnormalities in Region of Cloaca and Bladder It will be recalled that the urorectal fold has ordinarily completed the parti-

tioning of the cloaca by the time the cloacal membrane ruptures so that anal and urogenital orifices are independently established. Sometimes the part of the cloacal membrane occluding the anal outlet fails to break through. Such a condition may persist through gestation, presenting at birth a case of congenital anal atresia (Fig 356, C). If the closure is limited to the region of the

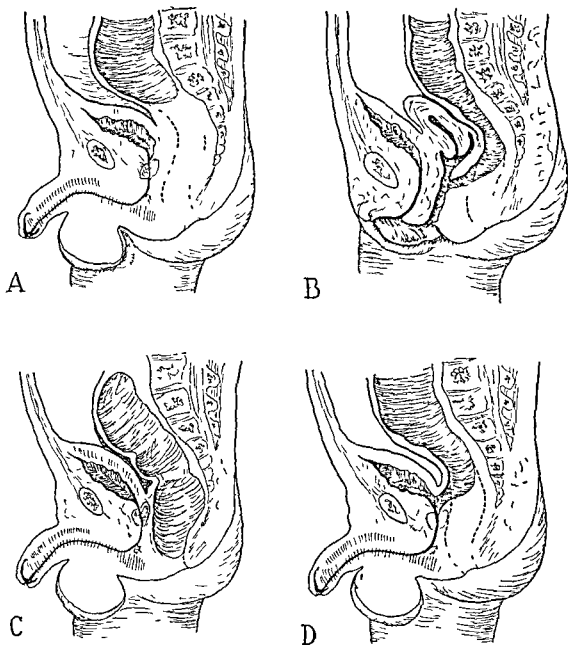


FIG 356 Anomalies due to disturbances in development of cloacal region (Redrawn from Corning) A, Anal atresia combined with obliteration of lower part of rectum B, Anal atresia combined with a rectovaginal fistula C, Uncomplicated anal atresia D, Anal atresia combined with rectovesical fistula

cloacal membrane and there is muscle from which an effective sphincter can be constructed, such cases lend themselves readily to surgical reconstruction. If, however, the atresia involves any considerable portion of the rectum (Fig 356, A) the problem of establishing an anal outlet in the normal location may involve such drastic surgery that resort to a colostomy is indicated.

In cases of anal atresia in female infants there is quite likely to be an open-

ing from the rectum into the vagina (Fig 356, B) Such cases of *rectovaginal fistula* present less acute problems because evacuation of the bowels can be carried out through the vagina This means that immediate surgical intervention as an emergency measure is unnecessary and that operation may be undertaken when conditions are deemed favorable Moreover, a two-stage operation may be planned if that seems to reduce the surgical risk or promise better results In the male an abnormal outlet for the rectum can be established only by way of the bladder and urethra (Fig 356, D) Obviously, such a *rectovesical fistula* does not provide an adequate rectal outlet and a prompt attempt to remedy the situation surgically is imperative

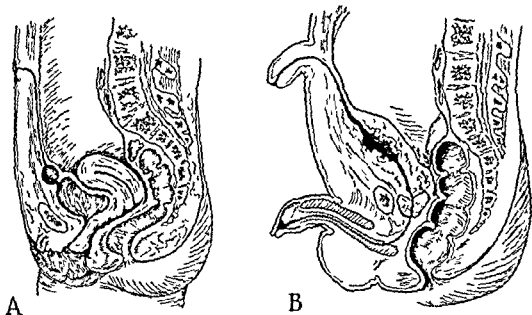


FIG 357 Two cases of umbilico-urinary fistula (Redrawn from Cullen "Embryology, Anatomy and Diseases of the Umbilicus," courtesy, W B Saunders Co)

Other types of congenital defects involving the bladder result from partial persistence of the lumen of the old allantoic stalk This may take a form starting as a local failure to obliterate the lumen Such a small, epithelially lined cavity tends to become fluid-filled, develop a thick connective-tissue capsule about itself, and become a characteristic nonmalignant cyst A cyst of this type may develop entirely without any internal connection with the bladder or external opening at the umbilicus, or it may be a dilated pocket on the course of a very narrow lumen persisting along the entire length of the urachus (Fig 357, A) Such a persistent allantoic lumen permits leakage of urine from the umbilicus and is appropriately known as an *umbilico-urinary fistula* The suggestive protuberance at the umbilicus in the case of simple umbilico-urinary fistula uncomplicated by cyst formation illustrated in Fig 357, B is a rare and functionally insignificant embellishment of the usual conditions

One of the rarer anomalies of the urinary system is *exstrophy of the bladder*, a condition in which the bladder lies open on the ventral body-wall Since this defect is usually combined with anomalous development of the sex organs it

seems better to discuss it in the final section of this chapter which deals with abnormalities of the external genitals

INTERNAL REPRODUCTIVE ORGANS

Indifferent Stage One of the striking things in the development of the reproductive system is the condition which at first exists as to sexual differ-

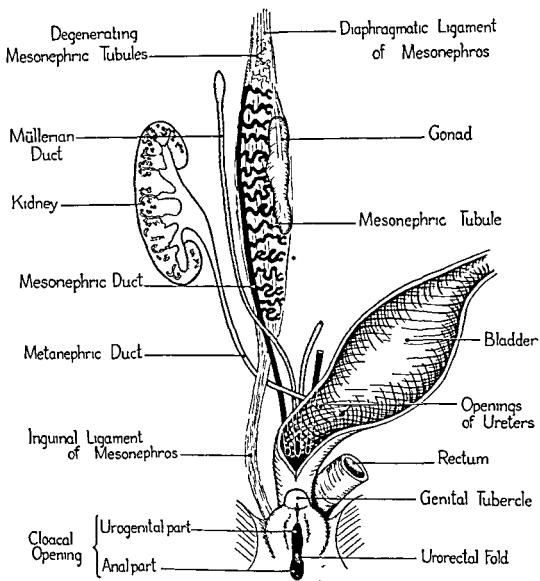


FIG. 358 Schematic diagram showing plan of urogenital system at an early stage when it is still sexually undifferentiated (Modified from Hertwig)

entiation. One might expect that reproductive mechanisms as unlike as those of adult males and females would be sharply differentiated from one another from their earliest appearance. Such is not the case. Young embryos exhibit gonads which at first give no evidence as to whether they are destined to develop into testes or ovaries. Along with these neuter or indifferent gonads there is present a double set of sexual duct systems. The male ducts are not developed primarily as reproductive ducts, but are appropriated from the regressing mesonephros, some of the mesonephric tubules becoming connected

with the developing gonad and the mesonephric duct being used as a discharge passage for the sex cells (See ducts in solid black in Fig 358) The female (Mullerian) ducts develop independently alongside the mesonephric ducts and the two duct systems are for a time present together (Fig 358) If the embryo is destined to become a male, the potentially female ducts remain rudimentary and the appropriated mesonephric ducts and tubules undergo further growth and differentiation to give rise to the duct system of the testes (Fig 361) If the embryo develops into a female, the Mullerian ducts form the uterine tubes, uterus, and vagina, and the male ducts become rudimentary

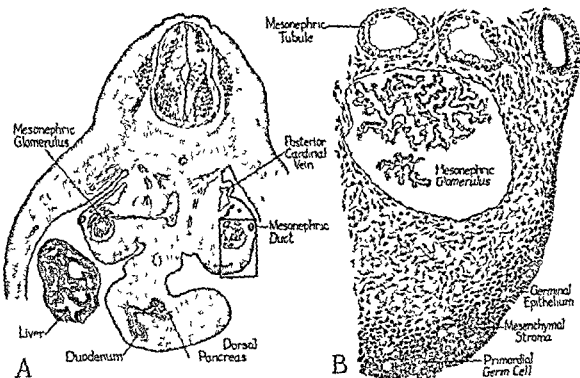


FIG. 359 Sections through indifferent gonad of 10 mm human embryo (University of Michigan Coll., EH 56) A, Projection drawing, $\times 30$, for topography B, Projection drawing, $\times 200$, of area indicated by rectangle in A

(Fig 362) In dealing with the embryology of the reproductive organs, therefore, conditions as they exist in the indifferent stage form a common starting point for the consideration of the later developmental changes in either sex

Origin of Gonads From their earliest appearance the gonads are intimately associated with the nephric system. While the mesonephros is still the dominant excretory organ, the gonads arise as ridge-like thickenings (gonadal ridges, germinal ridges) on its ventral border (Fig 359) Histologically the gonadal ridge consists essentially of a zone of closely packed cells covered by mesothelium. The mesothelial coat of the developing gonad is directly continuous with the mesothelium covering the mesonephros—is, in fact, merely a part of it stretched over the young gonad. It soon, however, begins to show characteristics which differentiate it from the adjacent mesothelium. It grows markedly thicker, and its cells round out and increase in size. Some of the

cells in the germinal epithelium as this modified layer of mesothelium is now termed, become conspicuously larger than their neighbors and push beneath the surface (Fig 359). These large cells are the primordial germ cells of the gonad. Considerable evidence has been adduced of late that these primordial germ cells do not arise *in situ* by the differentiation of mesothelial cells. It is maintained that they can be identified elsewhere in the body before they appear in the germinal epithelium, and that they migrate from their place of origin (yolk-sac entoderm, Fig 6) to settle down in the gonads and there rear their families. Whatever their earlier history may be, they are clearly recognizable in the germinal epithelium and its extensions into the deeper parts of the gonads in embryos of the sixth week.

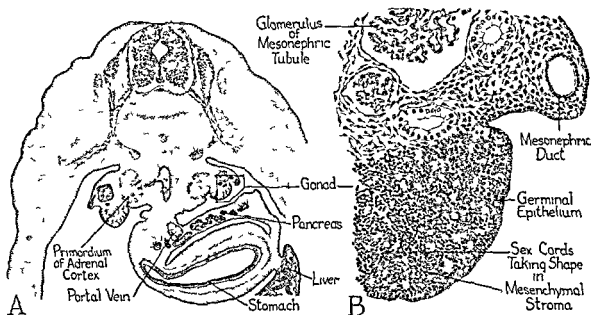


FIG 360 Sections through indifferent gonad of 13-mm (six-week) human embryo (Carnegie Coll., 841). A, Projection drawing, $\times 25$, for topography. B, Projection drawing, $\times 200$, of area indicated by rectangle in A.

Whether the gonad is to develop into a testis or an ovary, the cells of the germinal epithelium at first grow into the underlying mesenchyme and form cordlike masses (Fig 360). If the embryo is to be a male, these cords become increasingly sharply delimited and are eventually differentiated into the seminiferous tubules (Figs 369–371). In case the gonad develops into an ovary, the primordial cell cords tend to break up into cell clusters which become differentiated into primordial ovarian follicles (Figs 373–375). The divergent differentiation of the gonads in the two sexes will be discussed later in this chapter.

Sexual Duct System in the Male The ducts which in the male convey the spermatozoa away from the testis (except for the urethra) are, as we have seen, appropriated from the mesonephros—a developmental opportunism facilitated by the proximity of the growing testes to the degenerating mesonephros (Figs 361, 368). The mesonephric structures which are taken over by the testes are shown schematically in Figs 358 and 361.

EPIDIDYMIS Some of the mesonephric tubules which lie especially close to the testes are retained as the *efferent ductules* (Fig 5). They, together with that part of the mesonephric duct into which they empty (*ductus epididymidis*), constitute the epididymis (Fig 361). Cephalic to the tubules which are

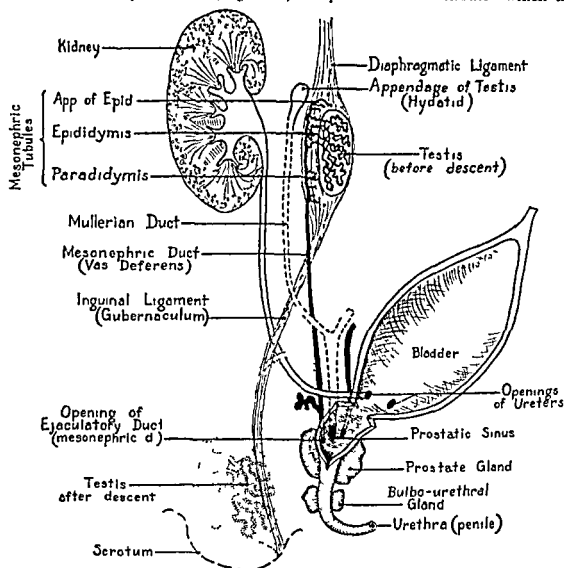


FIG 361 Schematic diagram showing plan of developing male urogenital system (Modified from Hertwig)

converted into efferent ductules a few mesonephric tubules sometimes persist in vestigial form as the "*appendix of the epididymis*" Caudal to the efferent ductules a cluster of mesonephric tubules almost invariably persists in rudimentary form as the *paradidymis*

DUCTUS DEFERENS, SEMINAL VESICLE, AND EJACULATORY DUCT Caudal to the epididymis the mesonephric duct receives a thick investment of smooth muscle and becomes the ductus (vas) deferens. A short distance before the vasa deferentia enter the urethral part of the urogenital sinus, local dilations appear in them which become elaborately sacculated and form the seminal vesicles (Figs 5, 383, 384). The short part of the mesonephric duct between the seminal vesicles and the urethra constitutes the ejaculatory duct. From

this point on the spermatozoa traverse the urethra, which thus serves as a common passageway to the exterior for both the sexual cells and the urine

Female Duct System The Mullerian ducts first appear in the latter part of the second month close beside the mesonephric ducts. They are the primordial structures in the female from which the uterine tubes, uterus, and vagina arise. It is thought possible by some investigators that phylogenetically

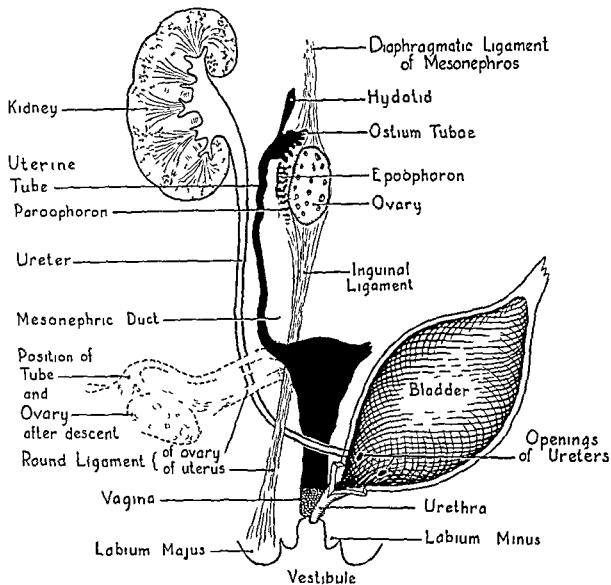


FIG. 362 Schematic diagram showing plan of developing female reproductive system (Modified from Hertwig)

the Mullerian ducts were split off from the mesonephric ducts. However this may be, ontogenetically in the mammals there is no recapitulation of any such process and the Mullerian ducts seem to arise independently by a process of infolding and then closing off of a groove in the coelomic mesothelium parallel to the mesonephric duct. The mesonephric ducts become well developed earlier than the Mullerian ducts and it is very easy to overlook the Mullerian ducts altogether in young specimens. By the time embryos have reached 20 to 25 mm in length, however, it is possible to locate them readily in sections or, with care, by dissection.

Where the fused distal ends of the Mullerian ducts make contact with the urogenital sinus, their potential lumen is packed solidly full of epithelial cells of the type which line the lumen higher up where it is not thus occluded. Meeting and merging with this cord of Mullerian duct cells (solid black in Fig 363, C) are cells (hatched area in Fig 363, C) growing back from the

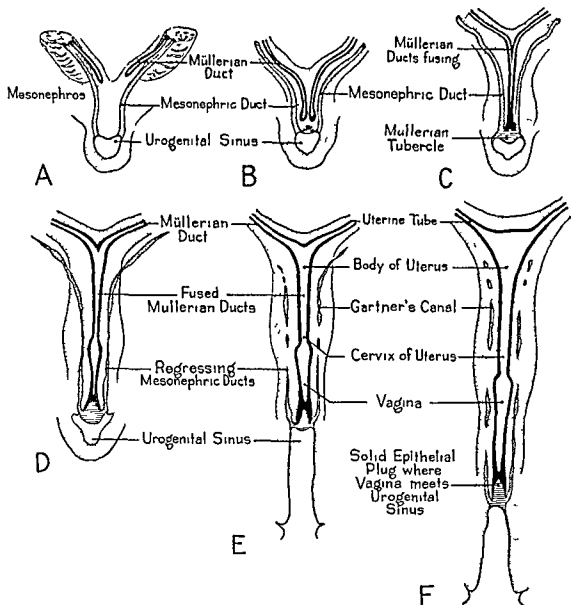


FIG 363 Fusion of Mullerian ducts to form uterus and vagina (Redrawn after Koff, Carnegie Cont to Emb, Vol 24, 1933) A, 23 mm B, 25 mm C, 32.9 mm D, 48 mm E, 63 mm F, 69 mm

epithelial lining of the urogenital sinus. The projection of this combined cell mass into the lumen of the urogenital sinus is known as the *Mullerian tubercle*. It is conspicuous only in the early stages of development before the solid cell mass of which it is composed opens up to connect the lumen of the upper part of the vagina with the urogenital sinus.

VAGINA In the formation of the distal portion of the vaginal lumen there

seems to be a tendency for the epithelial cells of urogenital sinus origin to proliferate very rapidly and to push in, replacing the epithelial cells in the lower part of the fused Mullerian ducts. How far this epithelial invasion extends into the lower part of the vagina is still a matter of controversy. The supplied lower part of the vagina in Fig 362 is intended merely to indicate the probability that epithelium spreads upward from the urogenital sinus for a way into the vagina, without any pretense of trying to indicate its precise limits. This uncertainty as to the epithelial lining should not be misconstrued to apply to the walls of the Mullerian ducts. Regardless of the secondarily

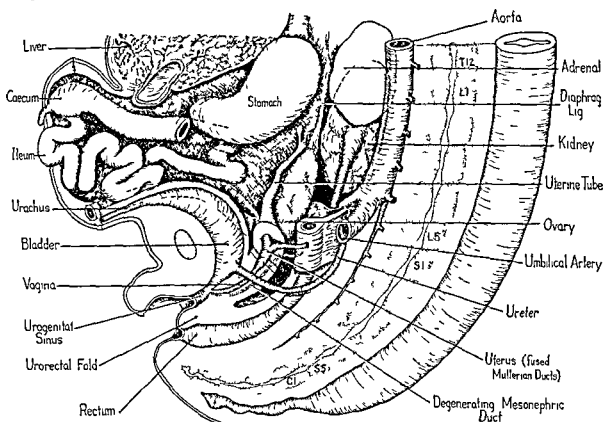


FIG 364 Semischematic drawing showing female reproductive organs at end of ninth week of development (Modified from Kelly and Burnam "Diseases of Kidneys, Ureters, and Bladder," courtesy, D Appleton-Century Co.)

changed point of epithelial transition, the Mullerian ducts should be thought of as meeting the urogenital sinus at the Mullerian tubercle. Where this tubercle later opens up to establish the vaginal orifice is clearly marked by the hymen (Fig 366). As we shall see when the development of the external genitals is considered, the originally deep and narrow urogenital sinus (Fig 364) becomes wider and less deep to form the so-called vestibule. This change brings the vaginal orifice into its definitive position much nearer the surface than it was in younger stages (Cf Figs 364-366 and Fig 4).

UTERUS In some of the primitive mammals fusion of the Mullerian ducts does not progress cephalad beyond the vagina. Such animals have paired uteri formed by enlargements of portions of the Mullerian ducts immediately cephalic to their entrance into the vagina. In all the higher mammals, fusion of the Mullerian ducts involves the caudal end of the uterus so that it opens

Where the fused distal ends of the Mullerian ducts make contact with the urogenital sinus, their potential lumen is packed solidly full of epithelial cells of the type which line the lumen higher up where it is not thus occluded. Meeting and merging with this cord of Mullerian duct cells (solid black in Fig 363, C) are cells (hatched area in Fig 363, C) growing back from the

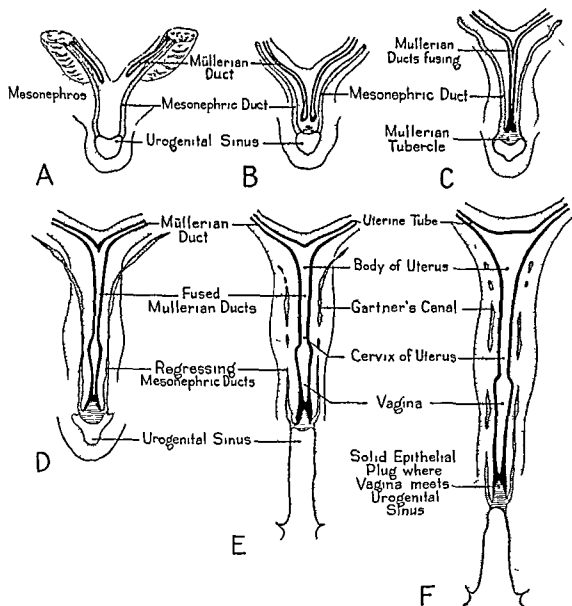


FIG 363 Fusion of Mullerian ducts to form uterus and vagina (Redrawn after Koff, Carnegie Cont to Emb, Vol 24, 1933) A, 23 mm B, 25 mm C, 32.9 mm D, 48 mm E, 63 mm F, 69 mm

epithelial lining of the urogenital sinus. The projection of this combined cell mass into the lumen of the urogenital sinus is known as the *Mullerian tubercle*. It is conspicuous only in the early stages of development before the solid cell mass of which it is composed opens up to connect the lumen of the upper part of the vagina with the urogenital sinus.

VAGINA In the formation of the distal portion of the vaginal lumen there

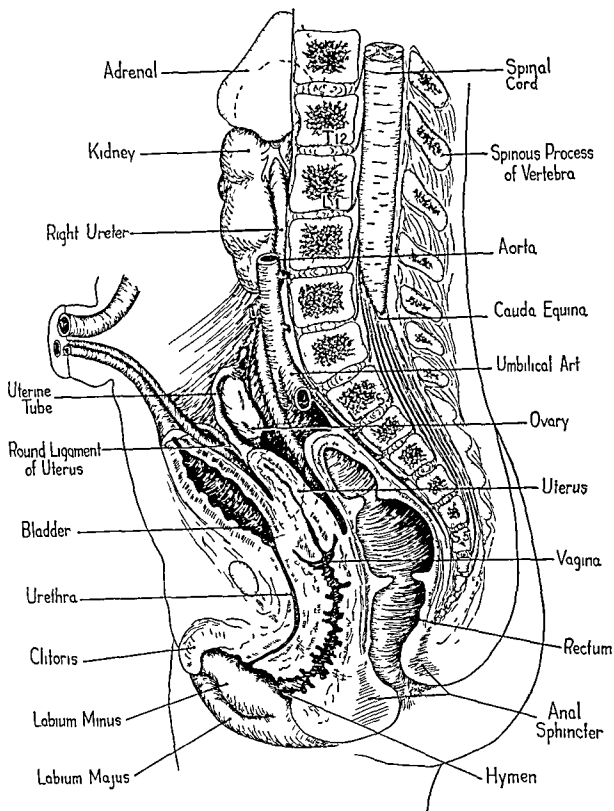


FIG 366 Female reproductive organs in a fetus at full term. (Modified from Kelly and Burnam "Diseases of Kidneys, Ureters, and Bladder," courtesy, D Appleton Century Co.)

into the vagina in the form of an unpaired neck or cervix. Above the cervix there is great variation in the degree of fusion encountered in the different groups. In most animals which bear many young in a litter the fusion is carried only a short way beyond the cervix to form what is called a bicornate uterus. In most of the primates, including man, the Müllerian ducts are fused with each other throughout the levels incorporated in the uterus. This results in the formation of what is called a simplex type of uterus (cf Figs 363 and 3)

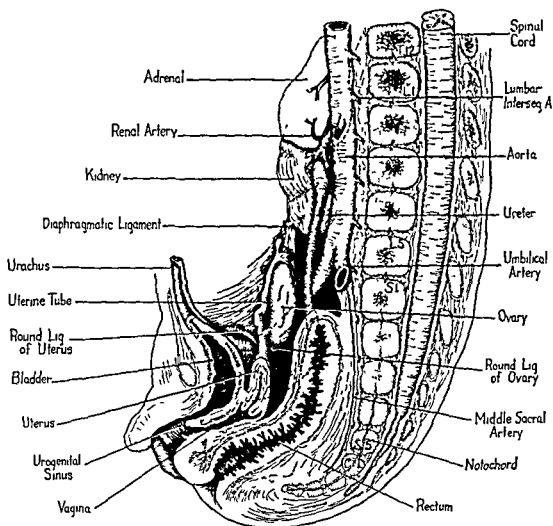
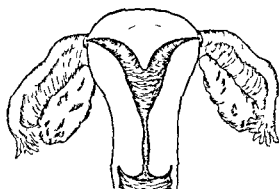
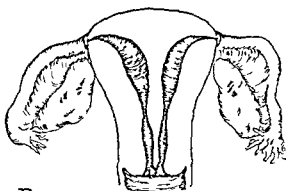


FIG 365 Female reproductive organs at end of twelfth week of development (Modified from Kelly and Burnam "Diseases of Kidneys, Ureters, and Bladder," courtesy, D Appleton Century Co)

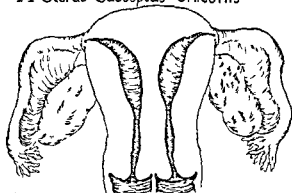
Although it is early established as a median primordium, the uterus attains its characteristic configuration only gradually. At first there is no obvious line of demarcation between the portion of the fused Mullerian ducts destined to form the uterus, and that which will give rise to the upper part of the vagina (Figs 363, C, 364). In the latter part of the third month the uterine region begins to be set off by the more robust character of its walls, and the beginning of the formation of vaginal fornices adjacent to the cervical portion of the uterus. During the fourth month the muscular and connective-



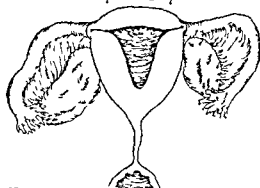
A Uterus Subseptus Unicollis



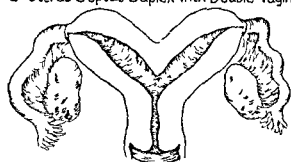
B Uterus Septus Duplex



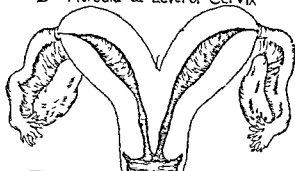
C Uterus Septus Duplex with Double Vagina



D Atresia at Level of Cervix



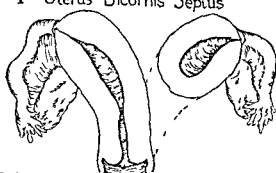
E Uterus Bicornis Unicollis



F Uterus Bicornis Septus



G. Uterus Didelphys with Double Vagina



H Uterus Bicornis Unicollis with one Unconnected Rudimentary Horn

FIG 367 Schematic diagrams of various types of abnormal uteri. All except D are differing types and degrees of duplicity resulting from departures from normal course of fusion of paired Mullerian ducts (Redrawn from Stander "Williams' Obstetrics," courtesy, D Appleton-Century Co.)

tissue coats of the uterus begin to be suggested by the arrangement of the mesenchymal concentrations. Toward the close of the sixth month the epithelium lining the uterus begins to send the primordial buds for the uterine glands into the underlying connective tissue. By term the glands are well molded but they remain relatively small and inactive until the time of puberty. The uterus at the time of birth has its cervical region quite characteristically formed. Its fundic portion, in contrast with the cervical portion, is strikingly small. In comparison with the adult uterus, the uterus of a fetus at term occupies a much more nearly vertical position in the body (cf Figs 366 and 4).

The growth of the fetal uterus during the last trimester of pregnancy is exceedingly rapid, presumably under the influence of the maternal hormones entering the fetal blood stream in the placenta. Not infrequently the uterine mucosa of newborn infants shows a congestion suggestive of premenstrual changes in an adult uterus, a condition which clearly implies responsiveness to maternal sex hormones. The fact that in the first few postnatal months the uterus actually decreases in size would seem to be a result of the withdrawal of this maternal hormonal stimulation.

UTERINE TUBES The part of the Mullerian duct between the uterus and the ovary on either side remains slender and forms the uterine (Fallopian) tube. Near its cephalic end, but not usually at the extreme tip, a more or less funnel-shaped opening develops (ostium tubae abdominale). In different forms the detailed configuration of the tubal ostium and its relation to the ovary are quite variable. In the sow, for example, there is a pouchlike dilation which almost completely invests the ovary, in the human female there is an elaborately fringed, funnel-shaped ostium which opens in the general direction of the ovary (Figs 3, 4). Whatever the morphological eccentricities of the ostium may be, they apparently make less difference in its efficiency in picking up the discharged ovum than one might suppose. Even in man, where the relation of the tubal ostium to the ovary is least intimate, abdominal pregnancies resulting from the fertilization of an ovum which the ostium failed to catch and start on its way to the uterus are comparatively uncommon.

As was the case with the uterus, the muscular and connective-tissue layers of the uterine tubes begin to be sketched in mesenchymal concentrations during the third month. By midpregnancy their characteristic arrangement can be clearly made out. The striking differentiation of the ampullar portions of the tube with its lumen broken up by complex folds (plicae, Fig 3) occurs mostly in the last third of gestation.

Abnormalities of Uterus and Vagina The more common abnormalities of the uterus and vagina are the result of variations in the extent or manner of fusion of the Mullerian ducts during their early development. Almost any degree of duplicity may be found and abnormal human uteri could be arranged in a series which would closely parallel the organ's evolutionary changes. Various degrees of partitioning of the fundus are among the more frequently encountered abnormalities (*uterus subseptus unicolis*—Fig 367, A,

rare is a completely paired uterus with each member of the pair having its own cervix opening into the corresponding member of paired vaginae (*uterus didelphys with double vagina*—Fig 367, G)

In addition to the foregoing types which follow the variations which one would expect to occur in the manner and extent of the fusion of originally paired primordia, there are other disturbances in which the departure from the normal developmental pattern has been along less predictable lines. There may, for instance, be a failure of the cervical portion of the uterus to develop (*atresia of the cervix*) so that a slender strand of tissue, completely without a lumen, is all that connects the fundus of the uterus with the vagina (Fig 367, D). A similar local atrophy occurring in one horn of a bicornate uterus may leave part of the horn in question completely cut off from the

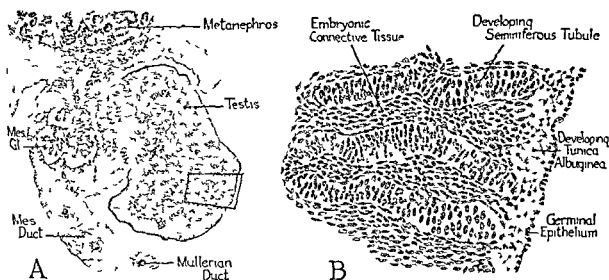


FIG 369 Testis of same 25-mm embryo from which Fig 368 was made

A, Topographical drawing through testis and regressing mesonephros (X 50)

B, Small area of testis, from place indicated in A (projection drawing X 200)

rest of the uterus (Fig 367, H). If this type of regressive process involves the uterine horns where the uterine tubes enter, *atresia of a uterine tube* may result. If such a condition is bilateral it, of course, results in sterility. Local atrophy may affect the vagina as well as the uterus, or the lower part of the vagina may fail to acquire a lumen and remain as a solid cord. Such *atresia of the vagina* seems more likely to occur in cases where there has been a profound general disturbance of sexual development as in some of the hermaphroditic or pseudohermaphroditic individuals. The conditions here mentioned by no means cover all the known anomalies of the uterus and vagina but they have been selected to indicate the range and type of disturbances which are most likely to be encountered.

Histogenesis of Gonads The establishing of the gonads on the ventro-medial borders of the mesonephroi and their structure in the early indifferent stages has already been discussed (Figs 6, 359). It is now pertinent to give attention to the later histological changes by which such indifferent gonads gradually become differentiated into testes or ovaries.

uterus septus duplex—Fig 367, B) Also occurring with relative frequency are uteri that show a tendency toward the bicornate type characteristic of so many of the mammals below primates In some cases only the fundic portion

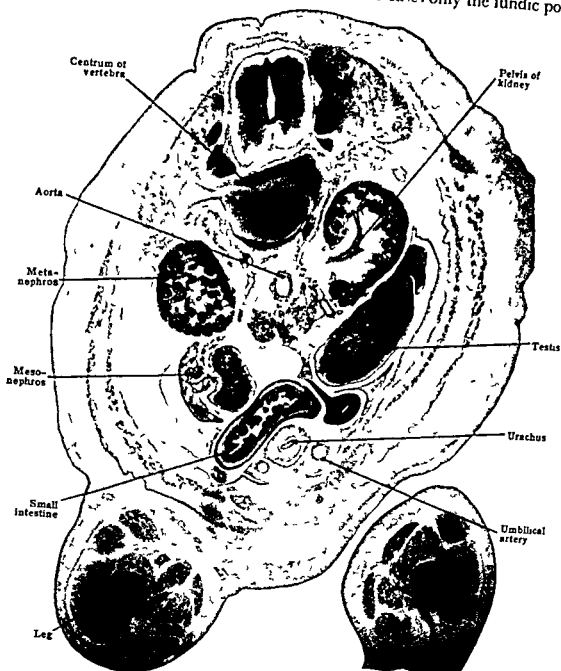


FIG 368 Photomicrograph ($\times 20$) of a cross section passing through the body of a male embryo of the eighth week at the level of the testis (University of Michigan Coll, EH 164, C-R, 25 mm) On the left the testis has been cut across its long axis, on the right the testis lies so that it is cut on a slant greatly increasing its apparent size

of the uterus is involved (*uterus bicornis unicollis*—Fig 367, E), in others the partition runs down into the cervical canal (*uterus bicornis septus*—Fig 367, F) Far more uncommon is complete partitioning of the uterus associated with a double vagina (*uterus septus duplex with double vagina*—Fig 367, C) Still more

of large epithelioid cells which are known as *interstitial cells*. As a matter of fact these peculiar cells are relatively more conspicuous at this early stage than they are postnatally—a somewhat startling situation in view of their suspected function of producing a male sex hormone.

By the middle of pregnancy the general architecture of the testis is well established. The original testis cords have each split into three or four daughter cords which may now properly be called *seminiferous tubules*. These tubules tend to be in the form of loops, with the limbs of the loop uniting in a slender

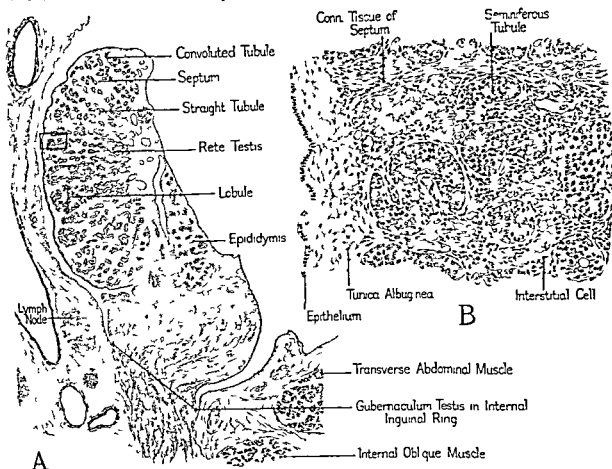


FIG 371 Testis of 20-week human embryo (University of Michigan Coll., EH 31, C-R, 180 mm) A, Topographical projection drawing, $\times 10$ B, Small area of testis, from place indicated in A, projection drawing, $\times 150$ (Cf. dissection drawn in Fig 377, A)

straight portion (*tubulus rectus*) discharging into the rete (Fig 5, B). The tubules derived from a single testis cord are quite sharply set apart from similar neighboring groups by connective-tissue septa which divide the organ into compartments (Fig 371, A). The young seminiferous tubules at this stage show no lumen, being composed of solid cords of potential germ cells. Among them are occasional cells which are definitely larger than their fellows, and which have a clear cytoplasm making them stand out strikingly in microscopical sections (Fig 371, B). These large cells probably should be regarded as potential germ cells which have started to differentiate precociously. They seem to undergo degeneration without ever becoming involved in the formation of spermatozoa. The definitive spermatogonia apparently arise much

TESTIS If an individual is destined to become a male, the cords of potential sex cells which were but vaguely defined in the gonads of the indifferent stage (Fig 360) become much more sharply delimited from the intervening embryonic connective tissue (Fig 369). They may now properly be called *testis cords*. At the same time there is developed directly beneath the germinal epithelium a conspicuous zone of young connective tissue. This is the start of a layer which in the adult is called the *tunica albuginea* (Latin, albus = white) because it is composed of such densely interwoven white fibrous connective tissue. The developing ovary shows a much less conspicuous layer of connective tissue in the corresponding zone under its germinal epithelium (cf Figs 369, 373).

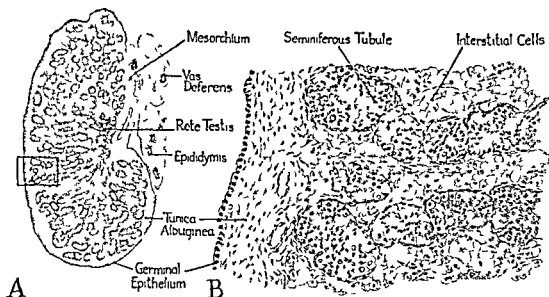


FIG. 370 Testis of a 14-week human embryo (University of Michigan Coll., EH 145, L, C R, 104 mm) A, Topographical drawing, $\times 20$ B, Small area of testis from place indicated in A, projection drawing, $\times 150$

By the fourth month of development (Fig 370) the testis has lost the original elongated, more or less spindle-shaped, configuration characteristic of the early gonad, and become more rounded and compact. At the same time its original broad attachment to the mesonephros is reduced to a mesentery-like attachment known as the *mesorchium*. Internally the testis cords have become sharply circumscribed by connective tissue. In the associated mesonephros only the duct, and the tubules at the level where they will be utilized in the formation of the epididymis, persist without extensive regressive changes. Already a marked mesenchymal concentration about the mesonephric duct foreshadows the heavy investment of smooth muscle which is indicative of its conversion into the *ductus deferens*. Adjacent to the depression (hilum) where the epididymis is attached to the testis, embedded in the connective tissue between the seminiferous tubules and the efferent ductules, are delicate-branching and anastomosing cords of cells which form the primordium of the meshwork of slender ducts, which will constitute the adult *rete testis*. In the connective tissue between testis cords are conspicuous masses

of large epithelioid cells which are known as *interstitial cells*. As a matter of fact these peculiar cells are relatively more conspicuous at this early stage than they are postnatally—a somewhat startling situation in view of their suspected function of producing a male sex hormone.

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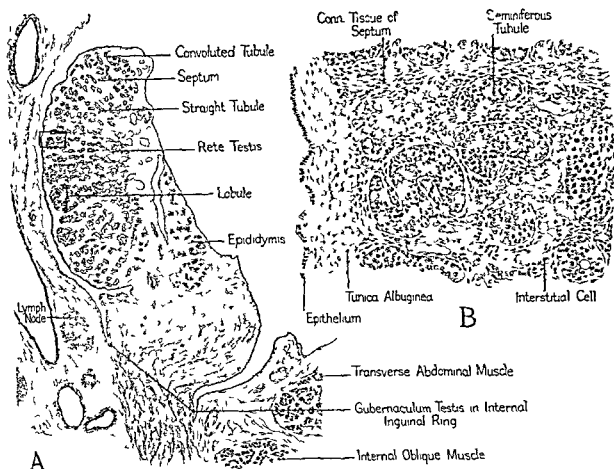


FIG 371 Testis of 20-week human embryo (University of Michigan Coll., EH 31, C-R, 180 mm) A, Topographical projection drawing, $\times 10$ B, Small area of testis, from place indicated in A, projection drawing, $\times 150$ (Cf dissection drawn in Fig 377, A)

straight portion (*tubulus rectus*) discharging into the rete (Fig 5, B). The tubules derived from a single testis cord are quite sharply set apart from similar neighboring groups by connective-tissue septa which divide the organ into compartments (Fig 371, A). The young seminiferous tubules at this stage show no lumen, being composed of solid cords of potential germ cells. Among them are occasional cells which are definitely larger than their fellows, and which have a clear cytoplasm making them stand out strikingly in microscopical sections (Fig 371, B). These large cells probably should be regarded as potential germ cells which have started to differentiate precociously. They seem to undergo degeneration without ever becoming involved in the formation of spermatozoa. The definitive spermatogonia apparently arise much

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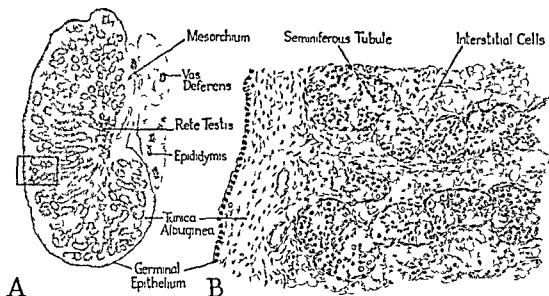


FIG 370 Testis of a 14-week human embryo (University of Michigan Coll., EH 145, L, C-R, 104 mm.) A, Topographical drawing, $\times 20$ B, Small area of testis from place indicated in A, projection drawing, $\times 150$

By the fourth month of development (Fig 370) the testis has lost the original elongated, more or less spindle-shaped, configuration characteristic of the early gonad and become more rounded and compact. At the same time its original broad attachment to the mesonephros is reduced to a mesentery-like attachment known as the *mesorchium*. Internally the testis cords have become sharply circumscribed by connective tissue. In the associated mesonephros only the duct, and the tubules at the level where they will be utilized in the formation of the epididymis, persist without extensive regressive changes. Already a marked mesenchymal concentration about the mesonephric duct foreshadows the heavy investment of smooth muscle which is indicative of its conversion into the *ductus deferens*. Adjacent to the depression (hilum) where the epididymis is attached to the testis, embedded in the connective tissue between the seminiferous tubules and the efferent ductules, are delicate branching and anastomosing cords of cells which form the primordium of the network of slender ducts, which will constitute the adult *rete testis*. In the connective tissue between testis cords are conspicuous masses

larger than their neighbors (Fig 374, B) and become surrounded by smaller cells to form *primary ovarian follicles* (Fig 375, B). By term these ovarian follicles are quite well developed (Fig 375, C) resembling closely the structure of the

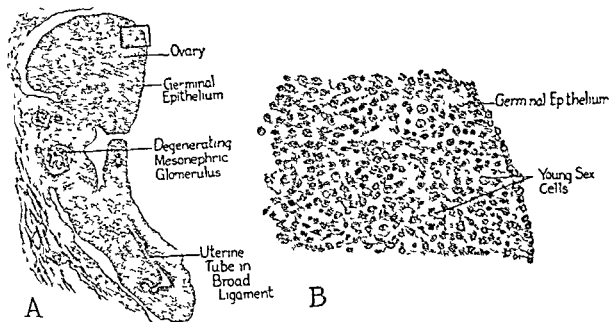


FIG 373 Enlarged views of ovary of 33-mm embryo shown in Fig 372 A, Projection drawing, $\times 40$, for topography in ovarian region B, Projection drawing, $\times 200$, of part of ovary indicated by rectangle in A

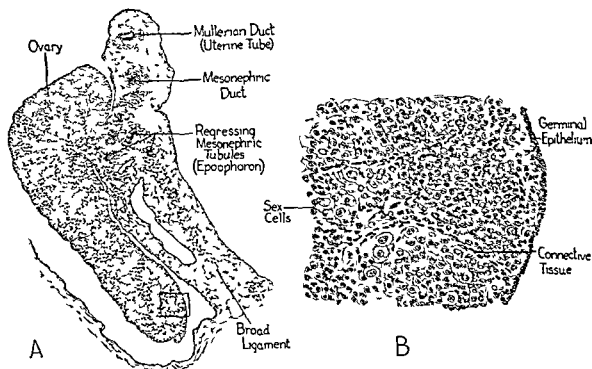


FIG 374 Ovary of an 11-week human embryo (University of Michigan Coll, EH 173, C-R, 65 mm) A, Projection drawing, $\times 30$, for topography B, Projection drawing, $\times 200$, of part of ovary indicated by rectangle in A

younger follicles in an adult ovary. Quite often they will even progress to the point of forming a small antrum. This is doubtless the result of their response to maternal gonad-stimulating hormones reaching the fetus by way of the

later from the cells in the cord which remain undifferentiated until puberty approaches. Except for the more regular radial arrangement of the cells of the seminiferous tubules and the appearance during the seventh month of the suggestion of a central lumen, there is little further change in the seminiferous tubules during intra-uterine life. During childhood the testis grows slowly in size but there is little change in the histological differentiation of the tubules until puberty approaches. The characteristic adult structure is then

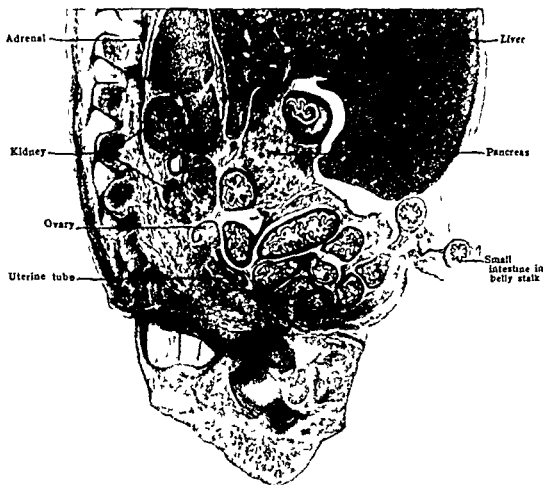


FIG. 372. Photomicrograph ($\times 10$) of parasagittal section of human embryo of ninth week passing through ovary and uterine tube (University of Michigan Coll., EH 22, C-R, 33 mm.)

rapidly attained. Conditions in the sexually mature testis have already been discussed in the section on gametogenesis (Chapter 2).

OVARY If an embryo is destined to develop into a female the earliest characteristic changes in the gonad are quite divergent from the differentiation in the male just discussed. In the young ovary there is a much less conspicuous zone of connective tissue beneath the germinal epithelium than that appearing in the corresponding location in the testis as the primordium of the tunica albuginea (cf Figs 369, 373). Instead of becoming more definite, the gonadal cords in the ovary become less distinct and the potential germ cells are scattered in the mesenchymal stroma. Some of these cells grow to be

Topographically the ovary gradually differentiates a cortical zone peripherally and a medullary area extending centrally from its mesovarial attachment. Into the medullary area radiate the vessels and nerves entering the ovary from the broad ligament. Lying partly in the medulla of the ovary and partly in the broad ligament and the mesovarium are rudimentary cell cords which constitute the so-called *ovarian rete* (Fig 375, A). They are homologous with the similarly located cellular strands in the testis which open out and become functional sperm ducts. The ovarian rete early undergoes regressive changes and normally leaves little or no vestige in the adult ovary. The cortex of the ovary is relatively more dense than the medulla, being closely packed with primordial ovarian follicles.

Later Changes in Relations of Internal Reproductive Organs Neither the testes nor the ovaries remain located in the body at their place of origin.

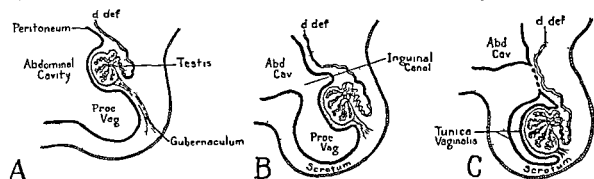


FIG 376 Schematic diagrams illustrating descent of testis as seen from side
Abbreviations d def, ductus deferens, Proc Vag, processus vaginalis (the diverticulum of the peritoneum pushed into the scrotal sac)

Before discussing their positional changes it is well to have clearly in mind their primary relations within the embryonic body. The urogenital system as a whole arises in the dorsal body-wall, covered by the mesothelial lining of the coelom (Fig 299, C-F). Later when the coelomic mesothelium of the abdominal region is reinforced by connective tissue the combined layer is known as the peritoneum. As to position of origin with reference to the body cavity, the urogenital organs may, therefore, be briefly characterized as retroperitoneal. This primary positional relationship is already familiar but it is emphasized again here because it is involved in many phases of the changes in position and relations undergone by the reproductive organs.

DESCENT OF TESTES When the mesonephros begins to grow rapidly in bulk, it bulges out into the coelom, pushing ahead of itself a covering of peritoneum. At either end of the mesonephros the peritoneum is, in this process, thrown into folds. One of them extends cephalad to the diaphragm and is known as the *diaphragmatic ligament of the mesonephros* (Fig 358). The other fold, which extends to the extreme caudal end of the coelom, becomes fibrous and is then known as the *inguinal ligament of the mesonephros*¹ (Figs 358, 361). The inguinal ligament is destined to play an important part in the descent of the testes.

¹ The inguinal ligament of the mesonephros of the embryo is in no way related to the inguinal ligament (Poupart's ligament) of adult anatomy.

placental circulation, for the tendency to antrum formation seen in the ovaries of female fetuses at term is absent during childhood, and reappears only as puberty approaches. It will be recalled that mention has already been made of a comparable response to maternal sex hormones on the part of the mammary glands and the uterine mucosa of term fetuses.

In all probability the follicles which are so conspicuous in the ovary of the newborn infant should be regarded as having developed precociously, and

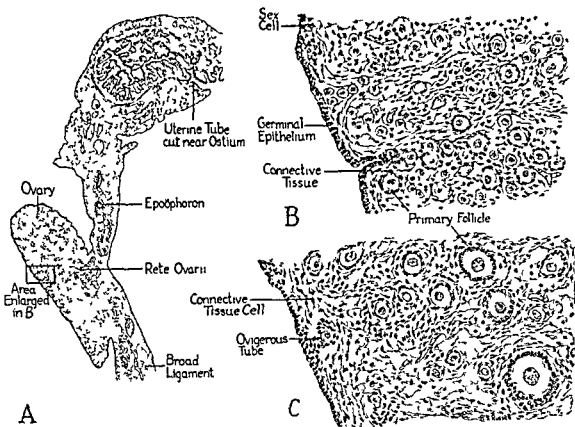


FIG. 375. Ovary at close of intra-uterine life. A, Projection drawing, $\times 10$, of ovary, uterine tube, and broad ligament of an eight-month fetus. B, Projection drawing, $\times 150$, of part of ovary indicated by rectangle in A. C, Projection drawing, $\times 150$, of a similarly located section from ovary of a newborn infant.

as being destined for early degeneration. The ova which are ripened during sexual maturity appear to be formed much later from the germinal epithelium or the cell cords derived from it. This view is, of course, in conflict with the older view that the ova in the ovary at birth are all the individual is destined to produce, and that they simply remain dormant until, with the onset of puberty, they begin to ripen a few at a time. As was pointed out in the section on gametogenesis, this difference of opinion as to the formation of new ova during sexual maturity is of more than theoretical interest. If additional ova are differentiated during maturity, the conservation of even small areas of germinal epithelium in surgical procedures involving the ovaries may well be of more importance than has hitherto been realized.

In the meantime a coelomic evagination is formed in the inguinal region of each side where the caudal end of the ligamentum testis is attached. Each of these peritoneally-lined extensions of the coelom is known as a *processus vaginalis* (Figs 376, 377, A). From the outer, connective-tissue layer of the processus vaginalis a fibrous cord, called the *scrotal ligament*, extends to the skin of the growing scrotum. The scrotal ligament is thus in effect a continuation of the ligamentum testis and the two of them together constitute the *gubernaculum* (Fig 377, B). As the processus vaginalis is deepened the scrotal ligament becomes shortened and broadened and ultimately blends into the general

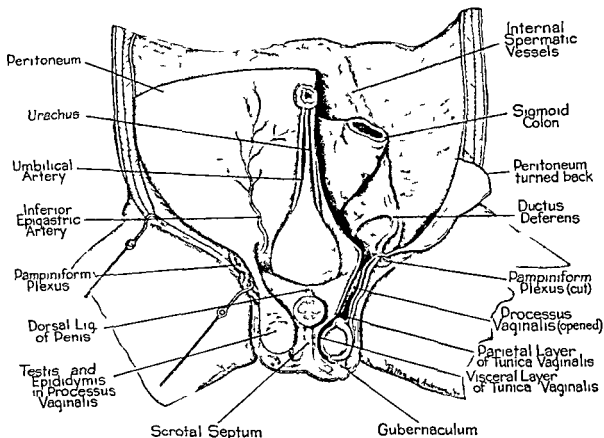


FIG 378 Dissection to show relations of testis in a fetus of ninth month (Modified from Corning) Left testis has been rotated through 90° to expose epididymis

connective-tissue layers of the scrotal wall (cf Figs 377, B, 378). By the time the processus vaginalis has attained its full depth the opening from the coelom into it has become smaller and its borders have been reinforced by connective tissue to constitute the internal inguinal ring. The definitive scrotal pouch is thus lined internally with the peritoneum of the processus vaginalis and covered externally by skin, and contains in between these two components thinned-out muscular and fascial layers continuous with those of the belly-wall. Even in the adult all the layers characteristic of the abdominal wall can be traced, in modified form, into the scrotum (Fig 379).

Coincidentally with the formation of the scrotal pouches, the testes and the mesonephric structures which are destined to give rise to the epididymis begin to shift their relative position farther caudad (cf Figs 376-378). By the fifth

We have already seen that when the testis starts to develop it lies within the peritoneal covering of the mesonephros which merely expands locally, adapting itself to the increased mass. As the testis grows still more, the mesonephros begins to decrease in size and the testis takes to itself more and more

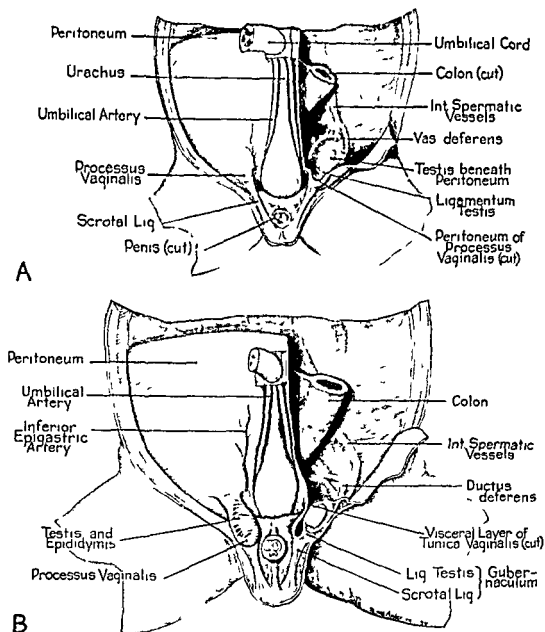


FIG 377 Dissections to show formation of processus vaginalis and descent of testes A, Fetus of about 20 weeks (C R, 180 mm, cf Fig 371) B, Fetus early in seventh month (about 280-290 mm C-R)

of what was, at first, the peritoneal coat of the mesonephros (Figs 368, 369, A). In all this process the testis is closely related to the inguinal ligament of the mesonephros. In effect the inguinal ligament fans out to include the growing testis as well as the shrinking mesonephros (Fig 361). When the testis has overshadowed the mesonephros the old inguinal ligament of the mesonephros is called the ligamentum testis and constitutes the cephalic portion of the gubernaculum.

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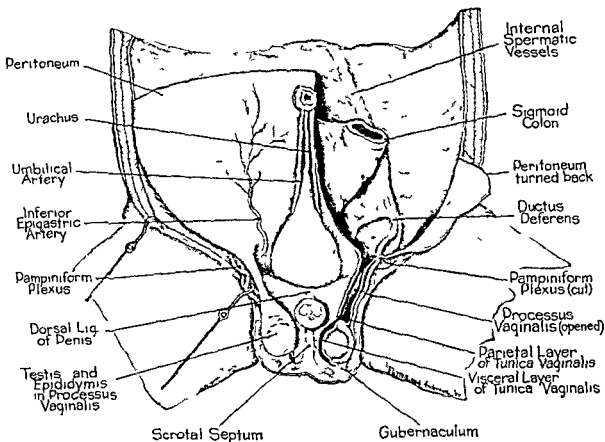


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month the testes lie close to the internal inguinal ring (Fig 371). Usually it is during the seventh month that the testes begin to pass through the inguinal ring, and ordinarily by the eighth month they have come to lie in the scrotal pouches. It would be more direct and vivid to say that the gubernaculum "pulls the testis down." Although the end-results of their association may seem to justify such a phrase, it would not be entirely correct. We would be overlooking the importance of differential growth. Failure of the gubernaculum to elongate in proportion to the growth of surrounding pelvic structure is in part responsible for any traction it may exert on the testis.

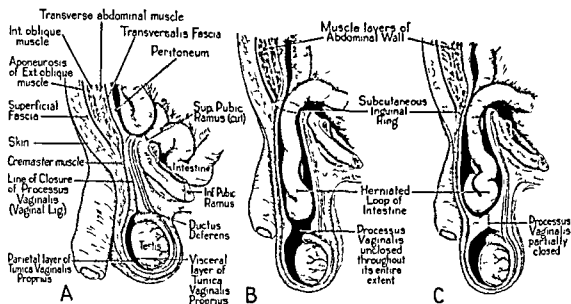


FIG 379 Diagrams illustrating congenital inguinal hernia (Modified from Callander "Surgical Anatomy," courtesy, W B Saunders Co) A, Normal adult anatomical relations, indicating manner in which abdominal wall structures are continued to form scrotal pouch, and showing line of closure of processus vaginalis (often marked by a fibrous strand called the ligamentum vaginalis) B, Congenital inguinal hernia in which processus vaginalis has remained unclosed throughout its entire length C, Congenital inguinal hernia in which processus vaginalis has closed for only a short distance just proximal to testis. Herniated intestine lies adjacent to spermatic cord but can not come into direct contact with testis. Clinically it is usually spoken of as a hernia of "funicular type" because of this relation to the spermatic cord.

In its entire descent, the testis moves caudad beneath the peritoneum. It does not, therefore, enter the lumen of the scrotal pouch directly but slips down under the peritoneal lining and protrudes into the lumen, reflecting a peritoneal layer over itself (Fig 376). This layer of reflected peritoneum is known anatomically as the visceral layer of the tunica vaginalis proprius. The remainder of the peritoneal sac which now lines the scrotal cavity is known as the parietal layer of the tunica vaginalis proprius (Fig 379, A). In most mammals, including man, when the testis has come to rest in the scrotal sac, the canal connecting the sac with the abdominal cavity becomes closed. In some of the rodents, however, the inguinal canal remains patent and the testes descend *into the scrotum only during the breeding season*, to be

retracted again into the abdominal cavity until the next period of sexual activity. Even in those forms normally exhibiting complete closure of the inguinal canal the obliteration of the opening is not uncommonly incomplete or structurally weak as evidenced by the occurrence of inguinal hernias (Fig 379). According to Callander's "Surgical Anatomy," the processus vaginalis is incompletely closed in some 50 per cent of male infants up to a month after birth.

FORMATION OF BROAD LIGAMENT In the young female embryo, as in the male, the mesonephros and the gonads arise retroperitoneally and bulge into the coelom carrying a fold of peritoneum about themselves (Fig 380, A)

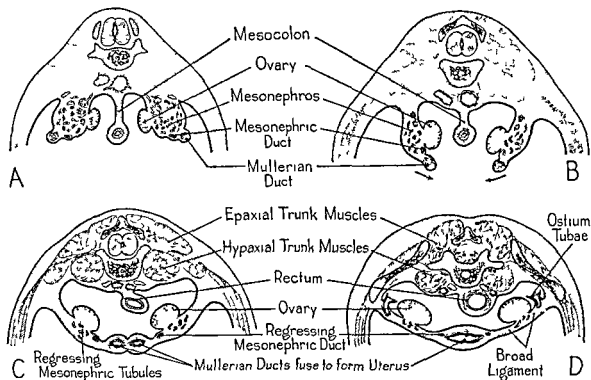


FIG 380 Schematic cross-sectional diagrams to show some of the main steps in formation of broad ligament

The mesonephros degenerate more completely in the female than in the male and their decreasing bulk leaves the peritoneal folds quite thin. At this stage they more or less resemble a pair of mesenteries suspending the Mullerian ducts in their ventral margins and the ovaries on their mesial faces (Fig 380, B). With further degeneration of the mesonephros and its replacement by fibrous tissue these folds become the part of the broad ligament supporting the uterine tubes.

Farther caudally in the body, where the Mullerian ducts fuse with each other in the mid-line to form the uterus (Fig 363), the supporting peritoneal folds coalesce medially to form the part of the broad ligament supporting the uterus (Fig 380, C, D). There is thus left between the dorsal body-wall and the broad ligament a bay of the peritoneal cavity. This bay at first extends far caudad toward the perineum (Fig 364). As the uterus and vagina grow, this bay becomes progressively shallower (cf Figs 364-366). Because of its

relations it is known in adult anatomy as the *uterorectal pouch* (pouch of Douglas) Postnatally, as the fundic part of the uterus attains mature proportions, it inclines ventrad, making the entrance into the utero-rectal pouch a much wider cone than it is in the newborn (cf Figs 366 and 4)

As a sequel to the obliteration, during development, of the original deep portion of the utero-rectal pouch, there are sometimes cystlike epithelial rests remaining in the tissue between the vagina and the rectum. In the male, also, there is a similar progressive obliteration of the homologous (rectovesical) pouch, and cystic epithelial remains of it may appear in the connective tissue between the rectum and the prostate

DESCENT OF OVARIES Although the ovaries move through far less distance than the testes, their change in position is quite characteristic and definite. As they increase in size, both the gonads and the ducts sag farther into the body cavity. In so doing they pull with them the broad ligament which, as it is stretched out, allows the ovaries, oviducts, and uterus to move caudally, laterally, and somewhat ventrally (Fig 362). The inguinal ligament of the mesonephros, which in the male forms the gubernaculum, in the female is embedded in the broad ligament. When the ovaries move caudad and laterad the inguinal ligament is bent into angular form. Cephalic to the bend it becomes the *round ligament of the ovary* (Figs 362, 3) and caudal to it, the *round ligament of the uterus* (Figs 362, 364-366, 4). It should be noted that the caudal end of the round ligament of the uterus is embedded in the connective tissue of the labium majus in a position homologous with the anchorage of the gubernaculum in the scrotal pouch of the male (cf Figs 361, 362). Thus the changes in position of the female reproductive organs are carried out in a manner quite different from those in the male. In both sexes the organs arise retroperitoneally, but in the male the testes slide along close to the body-wall beneath the peritoneum, while in the female the ovaries, oviducts, and uterus stretch the peritoneum into a mesentery-like structure which permits a certain latitude of positional change and at the same time serves as a supporting ligament.

Vestigial Structures in Genital Duct System In the conversion of the primordial sex-duct systems to their definitive conditions, some of the parts which are not utilized in the formation of functional structures persist in vestigial form even in the adult. Mention has already been made of the rudimentary mesonephric tubules which in the male persist as the *paradidymis* and the *appendix of the epididymis* (Fig 361). Traces of the old Mullerian duct system, also, can usually be found in the male. Attached to the connective tissue investing the testis there is sometimes a well-marked, vesicular structure called the *appendix of the testis* (hydatid) which represents the cephalic end of the Mullerian duct. The Mullerian ducts also leave a vestige at their opposite ends in the form of a minute diverticulum (prostatic sinus, or *vagina masculina*) which persists where the fused Mullerian ducts originally opened into the urogenital sinus (Fig 361).

In the female the ostium of the oviduct does not ordinarily develop at the

extreme cephalic end of the Mullerian duct. The tip of the duct is likely to persist in rudimentary form as a stalked vesicle (*hydatid*) attached to the oviduct (Figs 3, 362). The mesonephric tubules and ducts may remain recognizable to a variable extent. Usually there are embedded in the mesovarium a few blind tubules and traces of a duct, corresponding to the part of the mesonephric duct and tubules which in the male form the epididymis. These vestiges are called the *epoophoron* (Figs 3, 362). Less frequently, the more distal portion of the mesonephric duct (the part which in the male forms the vas deferens) leaves traces known as the *canals of Gartner* in the broad ligament close to the uterus and the vagina (Fig 380). These remains of the old mesonephric ducts and tubules are more important clinically than one might suspect from their inconspicuousness. As so frequently happens with vestigial structures, they are likely to become involved in pathological changes. In this case the most frequent disturbance is in the nature of a cystic enlargement. Starting with minute, epithelially-lined vesicles, rapid accumulation of fluid in the lumen may cause great distention of the surrounding tissues which in turn increases the irritation and provokes further accumulation of fluid. Not infrequently cysts starting in this manner attain considerable size and must be removed surgically.

EXTERNAL GENITALIA

The Indifferent Stages Still another thread in the story of the embryology of the reproductive system which has to be picked up separately is the development of the external genitals of the two sexes by divergent differentiation from a common starting point. It will be recalled that in very young embryos there is formed in the mid-line, just cephalic to the proctodaeal depression, a vaguely outlined elevation known as the cloacal or genital eminence. This is soon differentiated into a central prominence, the genital tubercle, which will ultimately become differentiated into the penis in the male (Fig 381) or into the clitoris in the female (Fig 382).² Along the caudal surface of the genital tubercle lie the paired genital folds extending toward the proctodaeum. Between the genital folds is a longitudinal depression into the caudal extremity of which the urogenital sinus opens. This opening (ostium urogenitale) was separated from the anal opening when the urorectal fold subdivided the primitive cloaca (Figs 353-355). Farther laterally, on either side of the genital folds, are paired vaguely outlined elevations known as the genital swellings, which become differentiated into the scrotal folds in the male, or into the labia majora in the female.

² Many writers have used the term 'phallus' for the conical mass of tissue which will become the penis or the clitoris. This does not seem an appropriate term for an indifferent primordium which may develop into either a male or a female structure. The term is borrowed from one of the sex cults of India in which the male sex organ (phallus) appeared as a prominent symbol. No one who has read of the usages of phallic festivals would associate the term phallus with anything other than an unequivocally male organ. It has therefore, seemed preferable to use the term genital tubercle for this primordium in spite of the fact that it is not infrequently used in a more restricted sense to refer only to the rounded tip which is the primordium of the glans penis or glans clitoridis.

Male Genitalia If the individual develops into a male, the growth of the genital tubercle is especially pronounced as it becomes elongated to form the penis. On the caudal surface of the penis the genital folds become conspicuously elevated and flank a deepening medial depression, known as the *urethral groove* (Fig 381, B). By the end of the third month the genital, or as they are

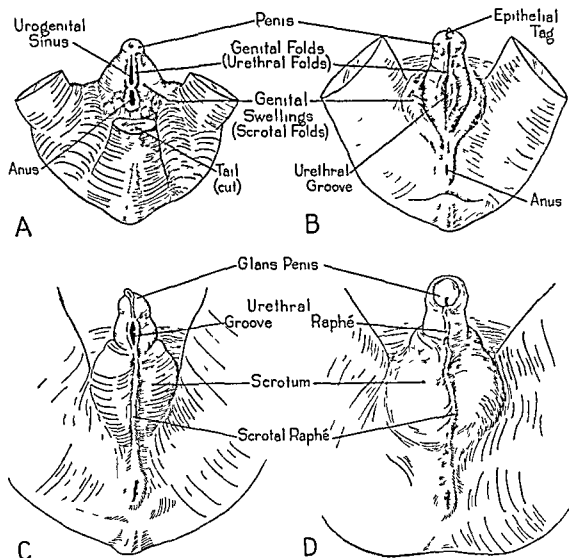


FIG 381 Stages in development of external genitals in male (Adapted from several sources, especially Spaulding, in *Carnegie Cont to Emb*, Vol 13, 1921) A, At seven weeks (17-20 mm) B, In tenth week (45-50 mm) C, Early in twelfth week (58-68 mm) D, Toward close of gestation

now more likely to be called, the *urethral folds* begin to close over the urethral groove much as the neural groove was closed to form the neural tube. In this manner the *male urethra* is lengthened by the addition of a penile portion. Thus, in effect, moves the urogenital outlet from its original location at the root of the penis (Fig 381, A) to the distal end of penis (Fig 381, D). The line of closure of the urethral groove remains marked by a scarlike vestige known as the *penile (urethral) raphe* on the under side of the adult penis. Along

the raphé the pigmentation of the skin, for some unknown reason, tends to be markedly more intense

Concurrently with the formation of the urethra, the *prepuce* is formed over the glans penis. The process is essentially the ingrowth about the tip of the penis of a potential fold of epithelium which separates off the preputial

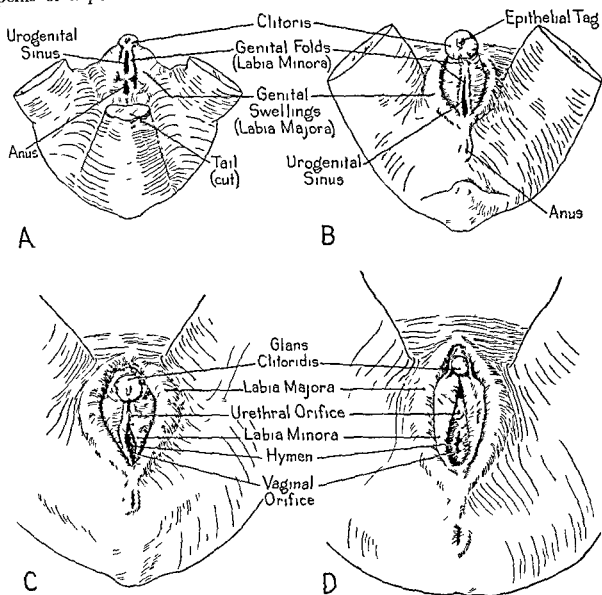


FIG 382 Stages in development of external genitals in female (Adapted from a number of sources, especially Spaulding, in Carnegie Cont to Emb, Vol 13, 1921) A, At seven weeks (17-20 mm) B, In tenth week (45-50 mm) C, At 12 weeks (75-80 mm) D, Toward close of gestation

covering of the glans. When the epithelium first grows in it is in the form of a solid sheet of cells which later splits to form the inner epithelial lining of the prepuce and the outer epithelial covering of the glans with the preputial space between.

The genital swellings are at first rather elongated folds situated in the inguinal region on either side of the developing penis (Fig 381, B). In older stages these folds develop most markedly in their caudal portions which expand and merge with each other in the mid-line on the anal side of the

root of the penis. The line of their fusion is the *scrotal raphé* which is continuous with the penile raphé, back through the perineal region. The manner in which these scrotal swellings are pouched out internally as bays of the peritoneal cavity has already been discussed in connection with the descent of the testes (Figs 376-379).

Female Genitalia In the female the genital tubercle becomes the *clitoris* and the genital folds become the *labia minora* (Fig 382). Although in young embryos there is for a time a urethral groove homologous with that in the male (cf Figs 381, B, 382, B), the parts of the genital (urethral) folds extending onto the under surface of the clitoris remain rudimentary and soon regress. Thus the urethral groove in the female is never deepened and closed over to form a urethra in the clitoris corresponding to the penile urethra of

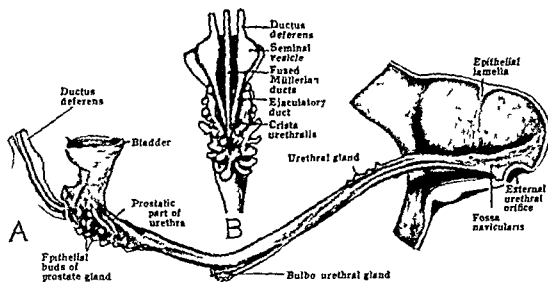


FIG 383 Reconstruction of urethral epithelium of a male human embryo of 65 mm (11 weeks fertilization age) (After Johnson, J Urology, Vol 4, 1920) A, Side view B, Dorsal view of prostatic portion

the male. In the adult female there is midventrally in the clitoris only an inconspicuous strand of vascular connective tissue (*pars intermedia clitoridis*) in a position comparable with that occupied by the penile urethra and the corpus cavernosum urethrae in the male. In the female, therefore, there is no secondary projection forward of the urethral orifice and just the prostatic portion of the male urethra is homologous with the entire urethra in the female.

It will be recalled that in the latter part of intra-uterine life the vagina, which was at first a very slender tube opening into the urogenital sinus (Fig 364), becomes greatly enlarged as compared with the size of the urethra (Figs 365, 366). At the same time the portion of the urogenital sinus distal to the vaginal orifice becomes very much broader and shallower, and it is this part of the old urogenital sinus which constitutes the so-called *vestibule* into which the urethra and the vagina of the adult open. Thus, in the female, the old urogenital sinus outlet, under a new name, persists in practically its original relations.

The *labia majora* are derived from the genital swellings and are homologous with the scrotum of the male. In the female these folds become heavily infiltrated with fat but they do not normally have any cavities within them comparable to the scrotal pouches. In rare instances there are rudimentary bays of the peritoneum extending for variable distances into the labia. Such anomalous homologues of the processus vaginalis of the male have been called the "*canals of Nuck*."

Accessory Sex Glands The so-called accessory sex glands are much more highly developed in the male than in the female. The principal ones are the seminal vesicles, the prostate gland, and the bulbo-urethral glands (Cowper's

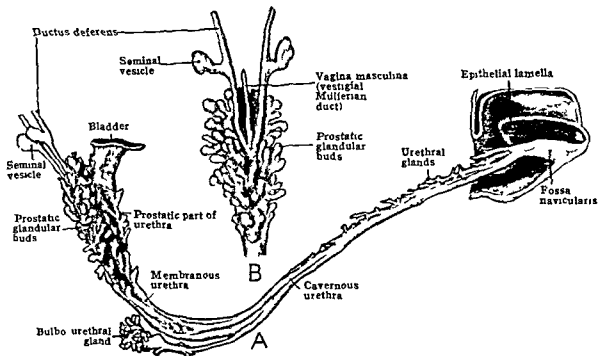


FIG 384 Reconstructions of urethral and related epithelial structures in male embryos of 130 mm. A, Lateral view of a reconstruction by Johnson. B, Dorsal view of prostatic portion of a similar model by Broman.

glands.) Less conspicuous are the multiple small urethral glands (glands of Littré) scattered along the length of the penile urethra.

The *seminal vesicles* arise early in the fourth month as lateral out-pouchings of the deferent (mesonephric) ducts a short distance above their entrance into the urethra (Fig 383). By the end of the fourth month sacculations of the primary outgrowths have begun to appear (Fig 384, A, B), and the vesicles thereafter rapidly increase in complexity until about the seventh month, by which time both the vesicles and the ampullar portions of the deferent ducts have practically reached their characteristic configuration.

The *prostate gland* arises from multiple outgrowths of the urethral epithelium into the surrounding connective tissue. These outgrowths develop in more or less localized groups corresponding to the lobes of the adult gland. The first tubules appear toward the end of the third month (Fig 383). Thereafter they rapidly increase in numbers, the careful studies of Lowsley (1912) indicating that upward of 50 separate outgrowths are usually formed

by the end of the fourth month. While the lobation of the gland is suggested from the first by the grouping of the epithelial outgrowths, it is not strongly marked until the last trimester of development when the fibromuscular septa begin to become well developed.

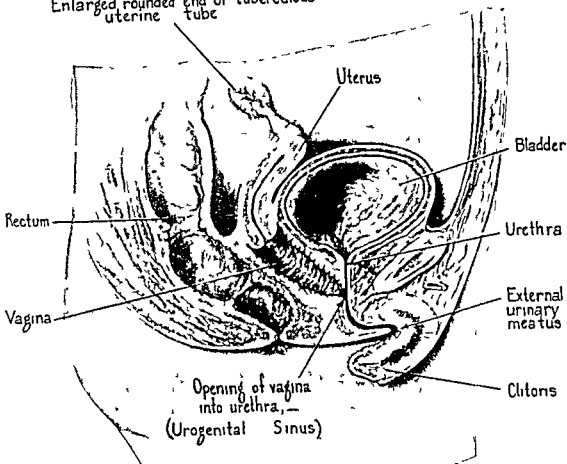
The *bulbo-urethral glands* (Cowper's glands) arise as paired epithelial outgrowths from the proximal part of the penile urethra. The initial buds appear during the third month and grow backward almost parallel to the urethra (Fig. 383, A). When the corpus cavernosum urethrae is formed, the ducts of Cowper's glands become embedded in its bulbar portion. The glands themselves develop adjacent to the membranous urethra in the loose connective tissue between the thick fibrous sheath of the urethral bulb and the urogenital diaphragm.

The seminal vesicles, the prostate, and Cowper's glands form a natural group from the functional standpoint in that all of them produce secretions which serve as a vehicle for the spermatozoa, and all of them are forcefully evacuated at the time of ejaculation. Although they develop at the same time and in a similar manner, the *urethral glands* (of Littre) belong in a different category functionally. They are small, compound tubo-alveolar glands which become activated during preliminary sexual excitement and produce a pre-coital, lubricating, mucous secretion. These glands make their appearance about the eleventh week as multiple separate outgrowths of the urethral epithelium (Fig. 383). In the fourth month terminal sacculations appear (Fig. 384) and by the final trimester of pregnancy the glands are well differentiated and histochemically the cells show evidences of the production of mucin.

In the female, there is no portion of the urethra homologous with the penile urethra of the male, but the *minor vestibular glands* should probably be regarded as corresponding with the urethral glands of Littre in the male. The seminal vesicles lack any homologues in the female. The curious cryptlike diverticula from the female urethra, sometimes called the *urethral glands of Skene*, are ill-developed homologues of the multiple prostatic glandular units of the male. In contrast, the homologues of the bulbo-urethral glands of the male are relatively more highly developed in the female. They are known as the *major vestibular glands* (of Bartholin). Their primordial buds arise during the latter part of the third month from the epithelium lining the urogenital sinus. They become sacculated during the fourth month, and like the other accessory sex glands show a characteristically differentiated morphology by the time of birth, although they do not get the major part of their growth until puberty approaches.

Abnormalities of External Genitals Like so many of the older terms in anatomy, the term *hermaphrodite* is drawn from classical mythology. It combines the names Hermes and Aphrodite to signify an individual who is a combination of the two sexes. Properly speaking, *true hermaphroditism* exists only when both testis and ovary are present in the same individual. It is a condition that is normal in many of the invertebrates but occurs only as an

Enlarged rounded end of tuberculous uterine tube



A



B



C

FIG 385 A case of pseudohermaphroditism (From H H Young "Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases," courtesy, Williams & Wilkins Co) A, Sagittal plan of pelvis B, Photograph of clitoris, pendent C, Photograph of clitoris raised to show its deeply grooved under surface

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disturbances the groove may remain unclosed throughout the shaft of the penis (Fig 386, B) or even as far as the perineal region (Fig 386, C)

A much rarer anomaly is *epispadias*, in which the penis is cleft along its cephalic face between the two corpora cavernosa. This is a very puzzling condition from the embryological standpoint for there is no stage of development when any such dorsal groove normally appears.

Occasionally, in either sex, there may be defective closure of the ventral body-wall in the mid-line from the umbilicus, through the pubic region, all

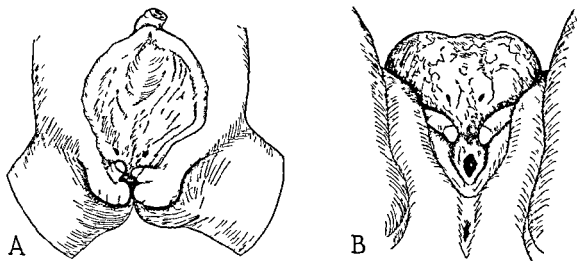


FIG 387 A, Exstrophy of bladder in a newborn male infant coexisting with splitting of penis (Sketched from specimen 5370 in the Rokitsansky Museum, Vienna) B, Exstrophy of bladder in a young female coexisting with splitting of clitoris (Redrawn from Schwalbe)

the way to the perineum. When this occurs a condition called *exstrophy of the bladder* is the usual sequel. What apparently happens developmentally is that the allantoic wall breaks through ventrally when it is not reinforced by a normally closing ventral body-wall. This leaves the bladder lying open on the belly surface, and at the same time, because the defect extends back through the pubic region, it results in a division of the penis or clitoris (Fig 387). The condition is commonly spoken of as doubling of the penis or clitoris. This is not a fortunate characterization for what really results is a halved organ which is molded around only one corpus cavernosum with the urethra and the corpus spongiosum urethrae wanting.

exceedingly rare anomaly in the higher mammals. There are a few authentic cases in man of what has been called true hermaphroditism on the basis of the microscopical recognition of both testicular and ovarian tissue. In most such cases, however, one or the other gonad is ill-developed and in no case has true functional competency of both gonads been demonstrated. The internal sex organs other than the gonads are likely to be symmetrically developed on the two sides and to tend definitely toward one sex or the other (Fig. 385, A). There are a few cases on record in which an ovary and a strongly developed Mullerian duct appear on one side, while a testis and strongly developed male ducts appear on the other. This condition is a variant of hermaphroditism.

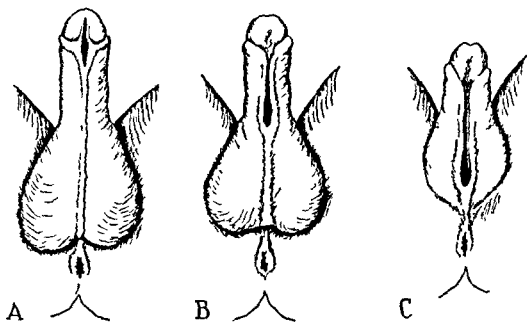


FIG. 386 Sketches showing varying degrees of hypospadias. The extreme case shown in C, combined with cryptorchidism, was sketched from specimen No 352 bis, in the Dupuytren Museum, Paris.

ism, called *bilateral gynandromorphism*. Whatever the variety of hermaphroditism, the external genitals are likely to be intermediate in their appearance, as are such secondary sexual characteristics as beard, breasts, voice, and pelvic configuration.

A condition designated as *false hermaphroditism* is encountered much more often than is true hermaphroditism. In such cases the gonads are definitely of one sex or the other, although they may be very poorly developed. The external genitals may be so ill-differentiated that designation of the individual's sex is impossible without an examination of the internal organs by exploratory operation. Not infrequently the external genitals are more strongly suggestive of the sex opposite to that exhibited by the internal organs (cf. Fig. 385, A, B).

Probably the commonest developmental anomaly of the male external genitalia is *hypospadias*. This is a condition in which the urethral groove has failed to close completely. Most common and least serious is a failure of the closure to reach all the way to the tip of the glans (Fig. 386, A). In more severe

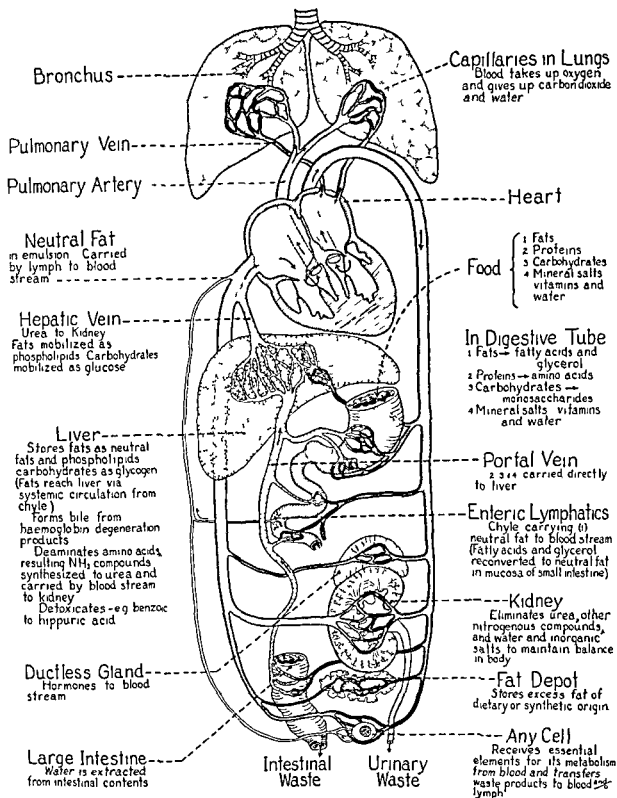


FIG 388 Schematic plan of adult circulation showing vascular plexuses in which some of the more important chemical interchanges take place

organs that carry on metabolism in the adult, development would be at an impasse

An embryo must, nevertheless, solve the problem of existence during the protracted time in which it is building up a set of organs similar to those of its parents. In the absence of a dowry of stored food in the form of yolk, the mammalian embryo draws upon the uterine circulation of the mother

Development of the Circulatory System

THE PLAN OF THE EMBRYONIC CIRCULATION AND ITS SIGNIFICANCE

The embryonic circulation is difficult to understand only when the meaning of its arrangement is overlooked. If one bears in mind certain fundamental conceptions as to the significance of the circulatory system in organic economics, and the basic morphological principle that any embryo must go through certain ancestral phases of organization before it can arrive at its adult structure, the changes in the arrangement of vascular channels during the course of development form a coherent and logical story.

In the embryo as in the adult, the main vascular channels lead to and from the centers of metabolic activity. The circulating blood carries (1) food from the organs concerned with its absorption to parts of the body remote from the source of supplies, (2) oxygen to all the tissues of the body from organs that are especially adapted to facilitate the taking of oxygen into the blood, and (3) waste materials from the places of their liberation to the organs through which they are eliminated (Fig. 388). One of the primary reasons the arrangement of the vessels in an embryonic mammal differs so much from that in the adult is the fact that the embryo lives under conditions totally unlike those which surround its parents. Its centers of metabolic activity are, therefore, different, and, since the course of its main blood vessels is determined by these centers, the vascular plan is different.

The organs which in the adult mammal carry out such functions as digestion and absorption, respiration, and excretion are extremely complex and highly differentiated structures. They are for this reason slow to attain their definitive condition and are not ready to become functional until toward the close of the embryonic period. Moreover, the conditions which surround certain of the developing organs during intra-uterine life absolutely prevent their becoming functional even were they sufficiently developed so to do. Suppose the lungs, for example, were functionally competent at an early stage of development. The fact that the embryo is reliving ancestral conditions in its private amniotic aquarium renders its lungs as incapable of functioning as those of a man under water. Likewise the developing digestive organs of the embryo are inaccessible to raw food materials. Further examples are not necessary to make it obvious that, were the embryo dependent on the same

the fertilized ovum of one species always gives rise to an individual of that species and to no other. The new individual will show detailed differences from its parents, differences which are capitalized in the slow march of evolution, but in a single generation these differences are never radical. We say that the offspring has inherited the structure of its parents. It does more: it inherits the tendency to arrive at its adult condition by passing through the same sort of changes which its ancestors underwent in the countless millions of years it took their present structure to evolve.

Applied to the development of the circulatory system of mammals this means that the earliest form in which it appears will not be a miniature of the adult circulation. The simple tubular heart pumping blood out over aortic arches to be distributed over the body and returned to the posterior part of the heart by a bilaterally symmetrical venous system—in short, the vascular plan which we see in young mammalian embryos (Fig. 74)—is essentially the plan of the circulation in fishes. When we realize this, we are not puzzled by either the appearance of a full complement of aortic arches or their subsequent disappearance to make way for a new respiratory circulation in the lungs. We see the march of progress from a logical beginning in ancestral conditions toward the consummation of fetal life with an organization like that of the parent.

In addition to the fundamental ground plan of the circulation of the mammalian embryo, recapitulations account for many transitory peculiarities. The formation of a conspicuous, though empty, yolk-sac with a complement of blood vessels almost as well developed as the vitelline vessels of animals well endowed with yolk is clearly a recapitulation of ancestral conditions. So, also, is the highly developed system of venous channels in the mesonephros. If the organ itself appears it brings with it its quota of vessels, no matter whether or not the organ is destined to degenerate later in development.

Whatever peculiarities may be impressed on the course of the circulation by the appearance of ancestral structures, or by the development of special fetal organs such as the yolk-sac and the placenta, the main blood currents will at any time be found concentrated at the centers of activity. Changes of these main currents as one center retrogresses and another becomes dominant must take place gradually. Large vessels become smaller, what was formerly an irregular series of small vessels becomes excavated to form a new main channel, but the circulation of blood to all parts of the body never ceases. Even slight curtailment of the normal blood supply to any region would stop its growth, any marked local decrease in the circulation would result in local atrophy or malformation, complete interruption of any important circulatory channel, even for a short time, would inevitably mean the death of the embryo.

FORMATION OF BLOOD CORPUSCLES (HEMOPOIESIS)

In the preceding section the arrangement of the blood vessels in relation to centers of functional activity was discussed. We are now ready to turn our

Utilization of this source of supplies depends on the development of a special organ which serves through fetal life and is then discarded. The embryo takes food not into its slowly developing gastro-intestinal tract but into its chorion, a membrane projected outside its own body and applied to the uterine wall to form, together with it, the placenta. The nutritive materials there absorbed from the maternal blood must be transported to the growing embryo by its own blood stream.

The use of food materials to produce the energy expressed in growth depends on the presence of oxygen. For growth there must be a means of securing oxygen and carrying it, as well as food, to all parts of the body. Nor can continued growth go on unless the waste products liberated by the developing tissues are eliminated. The blood of the embryo can not be relieved of its carbon dioxide and acquire a fresh supply of oxygen in the primordial cell clusters that will later become its lungs. It can not excrete its nitrogenous waste products through undeveloped kidneys. Its respiration and excretion, like its absorption of food, are carried out in the rich plexus of small blood vessels in the chorion. Here the fetal blood is separated from the maternal by tissues so thin that it can readily give up its waste materials to, and receive food and oxygen from, the maternal blood stream just as the mother's own tissues constantly carry on this interchange with the circulating blood. The placenta is thus the temporary alimentary system, lung, and kidney of the mammalian embryo. The enormous chorionic blood supply during fetal life, and the entire disappearance of this special arc of the circulation when the organism assumes adult methods of living, is a very striking example of the determination of vascular channels by the location of functional centers. We must not, however, overlook the fact that there are many other centers of activity in the growing embryo less conspicuous but equally important for its continued existence. Each developing organ in the embryonic body is a center of intense metabolic activity. During fetal life it must be supplied by vascular channels adequate to care for its growth.

But that is not all. Up to the time of birth each organ has been drawing on blood furnished with food and freed of waste materials by the activities of the maternal organism. At birth all this must change. Each organ essential to metabolism must be ready to assume its own active share in the process. Their vessels must be adequate to take care not only of the needs of these organs themselves but also of the functions these organs must now take over in maintaining the metabolism of the organism as a whole.

While the functional significance of the arrangement of the blood vessels is of primary importance, especially in understanding the progressive changes in vascular plan, there is another factor which we can not overlook. This factor is conservative, having to do with the things we inherit from our forebears. The goal of the embryonic period is the attainment of a bodily structure similar to that of the parents. Because it is so familiar, we accept with complaisance the remarkable fact that this goal is attained with absolute regularity. Accidents there may be, leading to defective development or malformation, but

1 per cent of the whites. They are unmistakable in stained smears because of the striking basophilic granules in their cytoplasm (Fig 391). They do not change in numbers in response to specific conditions as do other types of white cells, and their functional significance is not as yet understood.

BLOOD PLATELETS These are small basophilic protoplasmic bodies only 2 to 4 μ in diameter, usually present in blood films in small clusters. They are believed to liberate an enzyme concerned in bringing about the clotting of blood. The current view as to their origin is that they are fragments of the cytoplasm of certain giant cells (megakaryocytes) of the bone marrow.

Formation of the First Embryonic Blood Corpuscles in the Yolk-sac

It will be recalled that the first blood corpuscles to appear in the embryonic circulation arise in the blood islands of the yolk-sac. These primordial blood islands are clusters of mesodermal cells which, because they are destined to give rise both to vascular endothelium and to blood mother cells, may appropriately be called *hemangioblasts* (blood and blood-vessel formers). When such an island begins to differentiate its outer cells become flattened to form endothelial cells of the type characteristically lining blood vessels, and its more centrally located cells give rise to blood corpuscles and for this reason may be called blood-mother-cells, or *hemocytoblasts* (Fig 77, B). Some of the daughter cells of the hemocytoblasts soon lose their processes and become rounded to form blood corpuscles of a primitive type (Fig 77, B, C, 390, A). These first blood corpuscles are not like any of the types in adult circulating blood but they resemble somewhat the very young stages in the red-cell-forming (erythroblast) series seen in adult bone marrow (Compare the young embryonic corpuscles in Fig 390, A with the early erythroblasts in Fig 391). As a matter of fact the appearance of hemoglobin in the cytoplasm of these primitive embryonic corpuscles which is made evident by their staining reactions with eosin places them definitely in the red cell (erythrocyte) category. These early oxygen-carrying corpuscles serve the embryo for a time and then die out (Fig 389). The first of them are ready to enter the blood stream in the third week just as soon as it is set in motion by the developing heart. All of these first-formed corpuscles are nucleated. It is not until the sixth week that some of the red cells begin to extrude their nuclei before entering the blood stream. Embryos of around 12 to 13 mm in crown-rump length will usually show about 1 per cent of non-nucleated cells. During the next three weeks the number of non-nucleated reds increases very rapidly, upward of 90 per cent of the cells in the circulating blood being non-nucleated by the tenth week.¹

Succession of Blood-forming Centers in the Developing Embryo As development progresses, islands of hemangioblastic tissue appear in the mesenchyme in many places in the body and differentiate in the same general manner as that described for the yolk-sac islands. It was formerly contended that such islands within the embryonic body were formed only by direct spreading of the hemangioblastic tissue of the yolk-sac into the embryonic

¹ I am indebted to Dr. Elizabeth Thompson for permission to use these counts from a current study that as yet has not been published.

attention to blood as the transporting medium that flows through these supply channels

Components of Adult Blood (This section is for those students who have had no histology.) The blood of adult mammals is composed of a fluid vehicle, the *plasma*, in which are suspended formed elements of various types. These formed elements are either cells or protoplasmic bodies that were derived from cells. For purposes of description they may be grouped as red corpuscles, white corpuscles, and blood platelets.

RED BLOOD CORPUSCLES Human adult red blood corpuscles (erythrocytes, erythroplastids) are disk shaped bodies of surprisingly constant size (average diameter 7.6μ). When taken from normal circulating blood they are composed of cytoplasm only, the nucleus having been extruded just before the corpuscles are liberated from the blood forming centers into the blood stream. They are the oxygen carriers of the blood, their cytoplasm being saturated with a substance called hemoglobin which has the power of taking up oxygen from the surrounding medium and holding it in loose combination until it is yielded to tissues which are low in oxygen tension. The reds are the most numerous of the corpuscles. Their normal count is from five to five and a quarter million per cubic millimeter of blood in adult males, and about half a million lower in females.

WHITE BLOOD CORPUSCLES White blood corpuscles as a group can be distinguished readily from the reds by the fact that they have retained their nuclei. For differentiating the various types of white corpuscles from one another some of the special triple stains for blood are advantageous. One of the most widely used of these, Wright's stain, is a combination of methylene blue and eosin. The particular value of such a stain is that, in addition to staining acidophile granules a bright red with the eosin and basophile granules with the methylene blue, it also picks out and stains with a striking lilac color certain so-called neutrophile cytoplasmic granules that are characteristic of one of the types of white blood cells. It is this stain that was used in preparing the material on which the colored drawings of Fig. 391 were based, and the colors mentioned in the descriptions of blood cells in this section refer to material prepared with the same stain. The white corpuscles are usually divided into five types: lymphocytes, monocytes, and three kinds of granulocytes named on the basis of cytoplasmic granules which are acidophile, neutrophile, or basophile. In making routine laboratory examinations of blood all the white cells are first counted to give what is known as a *total white count*. In a normal adult this usually runs around 7,000 to 9,000 per cu. mm. In addition to the total white count a *differential white count* is regularly used. In a differential count the relative abundance of the several types of white cells is expressed in terms of the per cent of the total white count which each constitutes.

Lymphocytes Lymphocytes can be readily recognized by reason of the relatively large size of their nuclei. They so nearly fill the cells that the cytoplasm looks like a narrow, pale blue halo around the dark, purplish blue nucleus (Fig. 391). In young individuals lymphocytes will run as high as 35 to 40 per cent of the whites. In adults their count is ordinarily nearer 20 to 25 per cent. Their activities are not well understood but the way they tend to increase in certain diseases of long duration suggests they may perhaps be concerned in the neutralization of toxic materials.

Monocytes Monocytes are larger than the lymphocytes and tend to have more irregularly shaped nuclei and relatively more cytoplasm (Fig. 391). They are active phagocytes, particularly in any conditions involving the destruction of large numbers of red cells. They constitute 3 to 5 per cent of the white corpuscles.

Granulocytes The granulocytes are so named because of the presence of conspicuous, stainable granules in their cytoplasm. Most abundant are the *neutrophile granulocytes* which constitute some 60 to 70 per cent of all the white corpuscles. These cells tend to have irregularly shaped (polymorphic) nuclei (Fig. 391). They are actively phagocytic and their count will rise abruptly in the presence of infections, especially those due to bacteria of the types that cause pus formation.

Eosinophile granulocytes are about the same size as the neutrophiles but their larger cytoplasmic granules, brilliantly stained with eosin, make them readily recognizable (Fig. 391). They normally constitute only 3 to 5 per cent of the white blood cells but in certain allergic conditions and in infection with roundworm parasites (e.g., hookworm) they appear in greatly augmented numbers.

Basophile granulocytes are the least abundant of the blood cells, constituting only from 0.5 to

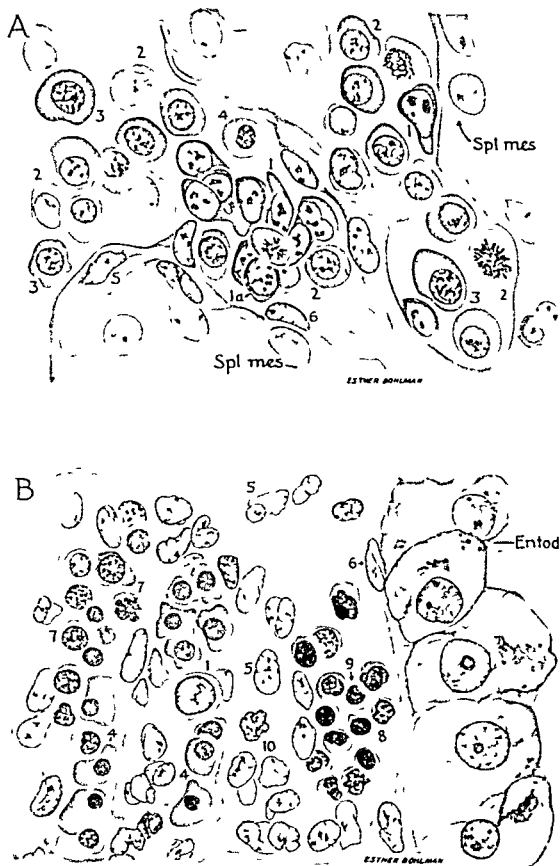


FIG. 390 Hematopoiesis in young human embryos (After Bloom and Bartelmez, *Am J Anat*, Vol 67, 1940) A, Section of yolk sac of embryo early in fourth week (University of Chicago Coll., H1516, 18 somites) The section is from a fold near outer surface as indicated by relations of splanchnic mesoderm (Spl mes) The tortuous vessels are filled with early stages in the formation of primitive erythrocytes The hemocytoblasts (1) form a compact mass of cells one is in mitosis Cells (2) and (3) are stages in development of primitive polychromatic erythroblasts which are differentiating toward primitive erythrocytes, (4)

B Section of yolk sac from human embryo early in eighth week (Maximow's H9) The endoderm (Entod) indicates inner face of yolk sac wall In addition to the primitive erythrocytes (cells 4) there are many polychromatophil definitive erythroblasts (cells 7, 7', 8) leading to formation of orthochromatic definitive erythroblasts (cell 9) Other cell types shown are a blast (1), mesenchymal cells (5), and a primitive macrophage (10)

body Most workers today believe, on the basis of fairly convincing experimental evidence, that hemangioblastic tissue can arise also, *in situ*, directly from the mesenchyme. This fact should by no means be taken to imply that

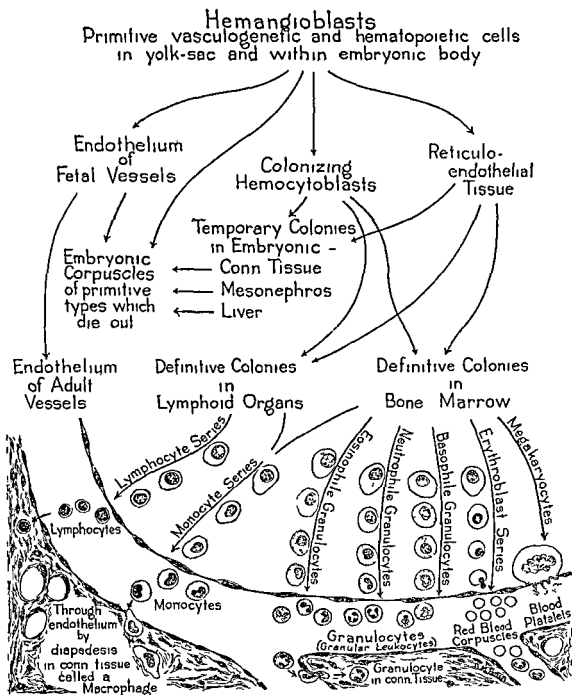


FIG 389 Chart showing derivation of various types of blood corpuscles in embryo and in adult

such islands of hemangioblastic tissue, once established, do not spread. On the contrary, sprouting of endothelial cells and proliferation and migration of cells with the capacity of producing other blood cells certainly plays a very important part in the development of the blood vessels and blood-forming

puscles without directly affecting the whites. Conversely, a lymphatic leukemia causes overproduction of lymphocytes without directly affecting the production of either erythrocytes or other types of white blood corpuscles. In view of these facts a reasonable standpoint at the present time would seem to be tentative acceptance of the monophyletic interpretation of the origin of blood cells in the embryo, with full recognition of the quasi-independent state attained in the adult by the different cell lines which originally arose from the common blood-nourish-cell or hemocytoblast. This viewpoint is graphically expressed in the diagram of Fig. 389.

Reticulo-endothelial Tissue. As the histological differentiation of the tissues of the growing body progresses there arises from the mesenchyme, wherever the formation of blood cells is going on, a particular kind of supporting tissue known as reticular connective tissue. A peculiarity of this tissue in such locations is the way it is directly continuous with the endothelium of blood vessels. In following under the microscope, a blood vascular channel in bone marrow or a lymphatic channel in a lymph node, the endothelium can be seen to become continuous with the meshwork of reticular connective tissue. At such points the vessel lumen is in connection with the irregular spaces in the reticular tissue, and blood cells moving through the vessel may lodge in these spaces, or cells newly formed from hemocytoblasts in the interstices of the mesh may enter the blood or the lymph stream. Because of this intimate association so general in areas where blood-cell formation is going on these two tissues in such locations are often designated together as reticulo-endothelial tissue or reticulo-endothelium. This association of endothelium, reticular tissue and enmeshed blood-forming cells is really only a slight elaboration of the hemangioblastic tissue of the embryo. The endothelium is little changed from its primordial condition, the reticular connective tissue is but a specialization of mesenchyme, and the blood-forming elements have merely taken on more specific characteristics than the original hemocytoblasts. The conception that the reticulo-endothelial tissue of older embryos and adults is merely a more differentiated phase of the primordial hemangioblastic tissue of the embryo under a new name is a most helpful one to have in mind in any problem involving blood formation or the behavior of blood-forming tissues under pathological conditions.

A peculiarity of reticulo-endothelial tissue is that many of its cells have the power of becoming actively phagocytic in response to the presence in the blood stream of foreign particulate matter. Since all the cells of this type in the body are called into activity together—regardless of whether they are reticulo-endothelial components of a lymph node, or the spleen, or the sinusoids of the liver or the maze of vascular channels in the bone marrow—the term *reticulo-endothelial system* has come into quite general use to cover all the reticulo-endothelial tissue in the body. Pathologists are naturally most interested in the phagocytic proclivities of this tissue. From the embryological standpoint the close similarity of reticulo-endothelial tissue and its associated hemocytoblasts to the hemangioblastic tissue of the embryo is of more importance

areas. The wandering blood-mother-cells involved in this process may be spoken of as *colonizing hemocytoblasts*, for they wander away from their place of origin, following along newly developed endothelial channels, and then settle down and raise families of blood corpuscles in a new location. They thus become established in a great variety of places in the growing body. Any area where there is a rich maze of small channels with slow blood flow seems suitable. Such centers, for example, appear in the loose young mesenchymal tissue of the head or the body-wall, in connection with the rich vascular plexus of the mesonephros, and conspicuously in association with the sinusoidal circulation of the young liver (Fig. 389). Each of these temporary foci of blood-cell formation has its period of active proliferation and then, as new centers are developed elsewhere, gradually ceases to be important in hemopoiesis. As the earlier centers regress and new ones become active, the corpuscles formed become of more highly differentiated types, gradually beginning to suggest in their appearance the various types of corpuscles which are destined to be formed in the adult.

Polyphyletic vs Monophyletic Interpretation of Blood-cell Origin

The appearance of progressively more widely differing types of corpuscles in the blood stream implies the differentiation of the parent cells from which the corpuscles have arisen. The manner in which this differentiation occurs has long been a matter of controversy among hematologists. One group sees in the appearance of a new type of corpuscle evidence that a new type of stem-cell has been differentiated directly from the parent mesenchyme. This school (the polyphyletic school) would, therefore, recognize an independent cell lineage for each major type of corpuscle. The opposing (monophyletic) view, which seems at present in the ascendancy, is that the parent cells of all types of blood corpuscles are merely differentiated descendants of the original hemocytoblasts which are thus the common stem-cell or blood-mother-cell of all types of corpuscles. Many of the striking phenomena seen under abnormal conditions seem best explained on such an interpretation as, for example, the production of red cells in the spleen of an adult following a severe hemorrhage. The spleen is one of the temporary centers of red-cell formation in the embryo, but before the end of the fetal period erythropoiesis ceases and the spleen becomes active in producing lymphocytes. The return to red-cell production when the blood has been depleted seems to imply the presence of hemocytoblasts which under these conditions of stress can still form erythroblasts.

At the same time it must be realized that the presence of hemocytoblasts which can be called into activity and form any type of cell needed, does not imply any lack of specificity in the parent cells of the several types of corpuscles. Once an erythroblast has been differentiated from a hemocytoblast, it will produce only cells of the erythroblast series. Moreover, it is sufficiently differentiated physiologically from the cells that produce white blood corpuscles so that it may be subject to a disease that does not affect them. For instance, pernicious anemia interferes only with the production of red cor-

puscles without directly affecting the whites. Conversely, a lymphatic leukemia causes overproduction of lymphocytes without directly affecting the production of either erythrocytes or other types of white blood corpuscles. In view of these facts a reasonable standpoint at the present time would seem to be tentative acceptance of the monophyletic interpretation of the origin of blood cells in the embryo, with full recognition of the quasi-independent state attained in the adult by the different cell lines which originally arose from the common blood-mother-cell or hemocytoblast. This viewpoint is graphically expressed in the diagram of Fig. 389.

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called *myeloblasts* because of their location in the bone marrow. The formative stages are much similar in the eosinophile, basophile, and neutrophile granulocytes. The granules in the young cells tend to be few in number and large

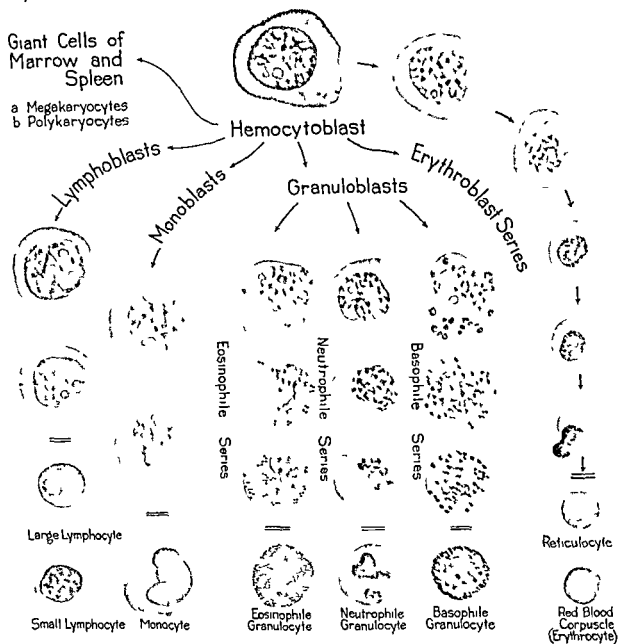


FIG. 391 Stages in histogenesis of blood corpuscles, arranged in developmental sequences (Adapted from several sources, primarily Osgood's "Atlas of Hematology" All cells $\times 1000$)

and irregular in size. They gradually become more abundant, taking on at the same time the size and staining reactions characteristic of the mature types (Fig. 391).

LYMPHOCYTES In the first part of intra-uterine life the formation of lymphocytes goes on at a low rate in all but the earliest of transitory hemopoietic centers. As development progresses and the lymphoid organs such as the thymus, the spleen, the lymph nodes, and still later the tonsils are laid down, they become the chief centers of lymphocyte production. The parent cell of

Definitive Centers of Blood-cell Formation What has been said covering the succession of blood-forming centers in the embryo, and the interpretation of reticulo-endothelial tissue as an extension and elaboration of the early hemangioblastic centers in embryonic mesoderm, should pave the way for an understanding of the definitive blood-forming centers. As conditions within the growing body change, we find that there is a gradual specialization of certain areas in the production of certain types of corpuscles.

RED BLOOD CORPUSCLES After having been formed first in the yolk-sac, then in many areas in connective tissue, and later in such parenchymatous organs as the liver, the mesonephros, and the spleen, the red cells are ultimately produced in bone marrow. Here again the centers of greatest activity change location, in this instance with the growth of the different components of the skeletal system. In general the bones with large cancellous areas are most actively involved. In older embryos and adults the ribs, the sternum, and the centra of the vertebrae are among the most active centers.

In the bone marrow the cells which differentiate toward red cells (cells of the erythroblast series) are found in clusters with all stages of differentiation mixed together. If the cells of the erythroblast series are arranged in developmental sequence (Fig. 391) the changes in their size and staining reaction are quite striking. The typical hemocytoblasts from which the erythroblasts, in common with other cell types, are derived, have a distinctly basophilic cytoplasm. One of the earliest indications that a descendent of this blood-mother-cell is committed to becoming an erythroblast is the appearance in the cytoplasm of pinkish areas. This variegated staining reaction (metachromatophilia) is indicative of the beginning of the accumulation of hemoglobin in the cytoplasm. As the series is followed the cytoplasm becomes increasingly acidophilic and more uniform in color (i.e., it becomes orthochromatic). Meanwhile with each cell division the new daughter cells become smaller and their nuclei become more compact. As they approach maturity they are called normoblasts. Finally, just before a cell is ready to be released into the blood stream, its nucleus is extruded. For a time when it has just recently entered the blood stream a young red blood corpuscle can be stained supravitaly with brilliant cresyl blue to show up a curious lacework of basophilic material in its cytoplasm. A cell exhibiting this reaction is called a *reticulocyte*. This is merely a designation tagging the red cell in question as a newcomer in the blood stream. The reaction is retained only briefly, some 1 to 2 per cent of reds showing it ordinarily. It is, nevertheless, an exceedingly valuable means of determining the effectiveness of measures which have been instituted to improve the red-blood-cell production of a patient.

GRANULOCYTES White blood cells resembling the immature granulocytes of an adult are formed along with red cells in some of the transitory hemopoietic centers such as the mesonephros and the liver. In older embryos and adults the granulocytes are formed in the bone marrow. The cells in the series of stages leading toward the fully differentiated granulocytes may most appropriately be called *granuloblasts*. Unfortunately, these same cells are very widely

called *myeloblasts* because of their location in the bone marrow. The formative stages are much similar in the eosinophile, basophile, and neutrophile granulocytes. The granules in the young cells tend to be few in number and large

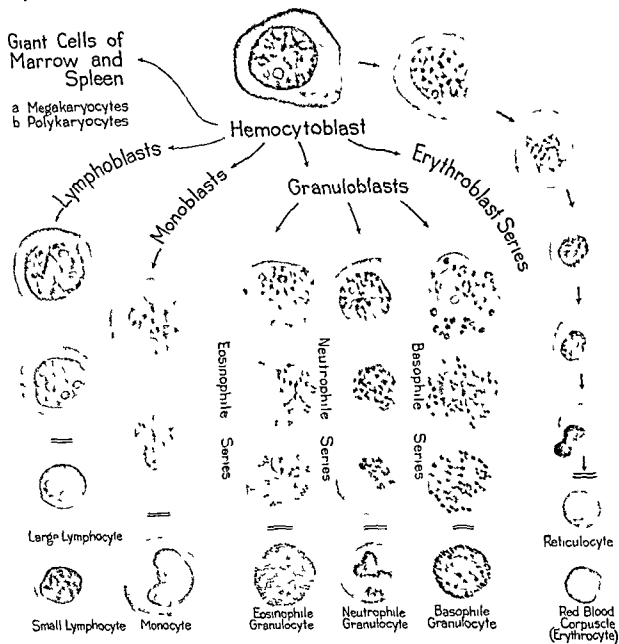


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the lymphocyte family at first differs very little from the hemocytoblast. When a lymphoblast does become clearly differentiated we can see that its cytoplasm is reduced in amount as compared with a hemocytoblast and that the quality of its staining reaction has changed from an opaque purplish blue to a clear pale blue which at times has almost a greenish tinge. The lymphocytes that are finally released into the circulation show further changes in the same direction. One of the most characteristic things about them is the very narrow cytoplasmic area surrounding the spheroidal darkly staining nucleus.

MONOCYTES The development of monocytes is one of the most controversial subjects in hematology. A book of the type of this one is certainly not the place to present the detailed technical evidence that might be advanced for and against the various views. All that seems expedient is to outline very briefly some of the views that are now widely accepted and to take them merely as a tentative working hypothesis with the frank recognition that they are quite likely to need revision as our knowledge increases.

One of the striking things about the hemangioblastic tissue of the very young embryo, and the reticulo-endothelial tissue which is its modified derivative in the more advanced stages of development, is its phagocytic proclivity. The young endothelial cells, and the reticulo-endothelial cells which form the borders of blood and lymph channels, can become swollen and take on large quantities of particulate matter injected into the blood stream. Such engorged cells are commonly spoken of as *fixed macrophages*. Under certain conditions these cells may round up, leave their littoral site of origin, and float away in the blood stream as free macrophages. From the blood stream these same cells may make their way through the endothelial lining of small vessels and wander out into the connective tissue. In the connective-tissue spaces their appearance will vary tremendously according to how long they have remained out of the circulation and how much they become engorged by phagocytosis. In this location most workers are now calling these cells *tissue macrophages*. Because of their different functional conditions they have been described under several different names (e.g., clasmatocyte, histiocyte, polyblast, resting wandering cell, ragiocrine cell). Fortunately, *histiocyte* is the only one of this array of names that is still being at all widely used to designate the cell here called a tissue macrophage. There seems little doubt that, in the embryo, cells with phagocytic potentialities arise in the manner described and that such cells once freed from their littoral position may be carried by the blood stream and lodge as colonizing monoblasts in new locations such as the developing lymphoid organs. Such a cell on the move in the circulation and not engorged by active phagocytosis would look like a young monocyte and would probably be so called in smear preparations made from blood drawn from peripheral vessels.

In addition to cells arising by this primitive method there is considerable evidence to indicate that in the later part of development and in the adult, monocytes arise from cells (monoblasts) derived directly from hemocytoblasts (Fig. 391). It is not unlikely that most of the cells we call monocytes in normal

adult circulating blood are so derived and that liberation of littoral cells from the reticulo-endothelial system occurs in the adult only under conditions of stress. These methods of origin are by no means as different as the names employed to designate the cells might seem to indicate. The cells of reticulo-endothelium are after all but hemangioblasts under a different name and there should seem nothing particularly strange in these totipotent cells producing phagocytic wandering cells by direct differentiation in the embryo and indirectly through cells we are pleased to call hemocytoblasts and monoblasts in the adult or by either method according to varying functional conditions.

GIANT CELLS OF BONE MARROW. There are two types of giant cells formed in bone marrow and less extensively in other hemopoietic centers. One of these cells possesses many small nuclei and is known as a *polykaryocyte*. Neither the functional significance of polykaryocytes nor their possible relation to other multinucleated cells such as the osteoclasts or the foreign-body giant cell is known. The other type of giant cell has a single large, many-lobed nucleus and is called a *megakaryocyte*. The megakaryocyte is believed to originate by the growth and modification of cells of the hemocytoblast stock. Neither giant cell leaves the hemopoietic centers to enter the circulating blood.

BLOOD PLATELETS. It is believed that the blood platelets arise in the cytoplasm of the megakaryocytes. Sprawling pseudopods of these giant cells in the bone marrow have been seen by Wright (1910) to push through the endothelium of small vessels. Where they project into the lumen these pseudopods contain basic staining particles about the size and appearance of the blood platelets seen in smear preparations. Fragmentation of the cytoplasm of these pseudopods is said to liberate the contained platelets into the blood stream.

ARTERIES

Derivatives of the Aortic Arches. In vertebrate embryos six pairs of aortic arches are formed connecting the ventral with the dorsal aorta. The portions of the primitive paired aortae that bend around the anterior part of the pharynx constitute the first (i.e., the most cephalic) of these aortic arches. In its course around the pharynx the first aortic arch is embedded in the tissues of the mandibular arch (Fig. 392, A). The other aortic arches develop later, in sequence, one aortic arch in each branchial (gill) arch caudal to the mandibular (Fig. 392, C-E). But in mammalian embryos we never find the entire series of aortic arches well developed at the same time. The two most anterior arches degenerate as main channels before the posterior arches have been established (Fig. 392, D, E). It should be noted, however, that their disappearance is neither abrupt nor complete as the schematic diagrams (Fig. 393) summarizing the changes in the aortic arches might lead one to believe. They break down as main channels, but leave behind a plexus of small vessels appropriated by the local tissues as their source of nutrition.

The early degeneration of the first two aortic arches, and the fact that the fifth arch never appears in mammalian embryos except transitorily as a vestigial vessel appended to one of the neighboring arches, leaves only the ventral

and dorsal aortic roots and the third, fourth, and sixth arches to play an important rôle in the formation of adult vessels

EXTERNAL CAROTID ARTERIES Study of the diagrams in Fig. 392 will make

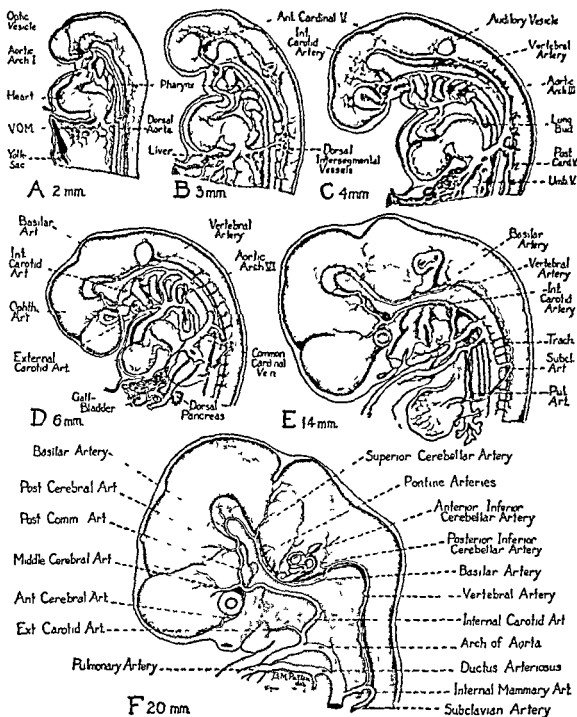


FIG. 392 Development of aortic arches and cerebral vessels in human embryos (Based, in part, on the work of Congdon)

apparent the manner in which the portions of the ventral aortic roots, which formerly acted as feeders to the first two arches, are retained as the external carotid arteries. These vessels, in part through the small channels left by the

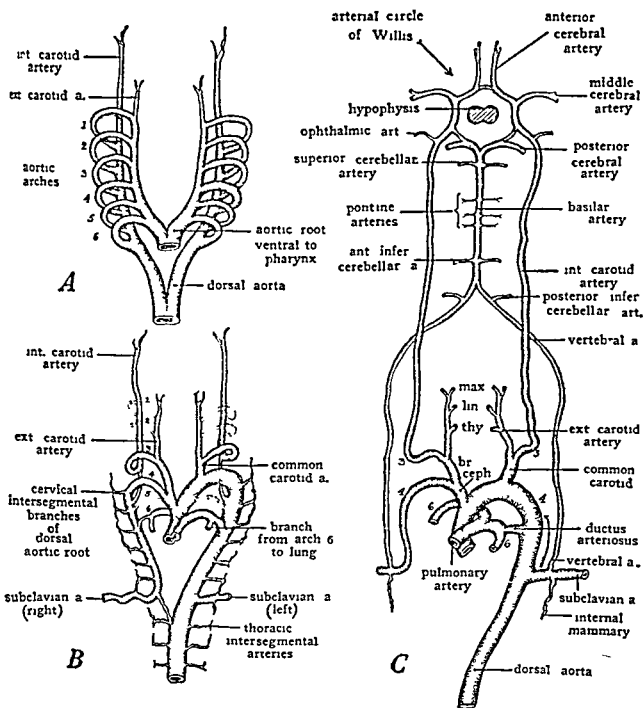


FIG 393 Diagrams illustrating changes which occur in aortic arches of mammalian embryos (Adapted from several sources) A, Ground plan of complete set of aortic arches B, Early stage in modification of arches C, Adult derivatives of aortic arches

Abbreviations br cep, brachio cephalic (innominate) artery, lin, lingual artery, max, maxillary artery, thy, thyroid arteries Fig 392 shows from another view, and less schematically, some of the changes summarized in this illustration Arrow in C indicates change in position of origin of left subclavian artery which occurs in the later stages of development

disintegration of the aortic arches with which they were originally associated, and in part through the formation of new branches to subsequently formed structures, nourish the oral and cervical regions Comparison of Fig 392, F and 395 will emphasize how early in development the major territory to be supplied by the external carotid artery becomes evident Its thyroid, lingual,

palatine, and maxillary branches all supply structures developing in maxillo-mandibular and hyoid arch regions of the embryo with which the primitive external carotid artery is associated. Secondary peripheral extension of the original external carotid territory is shown by the course of its occipital and temporal branches supplying muscles that have migrated into the cephalic region (Fig 191), bringing their blood supply along with them.

INTERNAL CAROTID ARTERIES The internal carotid arteries from their first appearance are closely associated with the developing brain. They are first formed as short cephalic prolongations of the dorsal aortic roots extending toward the forebrain (Fig 392, A-C). When the first and second aortic arches drop out, the dorsal aortic roots into which they originally discharged still persist, lengthening the channels which are being molded into the internal carotid arteries as we know them in the adult. When, a little later, that portion of the dorsal aortic root which lies between arch 3 and arch 4 dwindles and drops out, the third arch is left constituting the curved proximal part of the internal carotid artery (Figs 392, D, E, 393, 395). The part of the ventral aortic root which, from the first, has fed the third aortic arch persists practically without alteration as the common carotid artery.

ARCH OF THE AORTA The fourth aortic arch has a different fate on opposite sides of the body. On the left it persists as the arch of the adult aorta (Figs 392, 393). On the right the fourth arch forms the proximal part of the subclavian artery. With the enlargement of the left fourth aortic arch to form the main channel leading from the heart to the dorsal aorta, the dorsal aortic root on the right side becomes much reduced (Fig 393). Caudal to the level of the subclavian it drops out entirely. It will be recalled that the distal part of the sixth aortic arch also drops out on this side. This leaves the right subclavian communicating with the dorsal aorta by way of a considerable section of the old dorsal aortic root and the fourth aortic arch. In the adult, both the *distal part of this vessel formed by the intersegmental artery*, and its proximal part appropriated from the old aortic arch system, pass under the name of subclavian. The short section of the right ventral aortic root between the fourth and the sixth arch persists as the innominate (brachiocephalic) artery from which both the right subclavian and the right common carotid artery arise.

PULMONARY ARTERIES The sixth aortic arch changes its original relationships somewhat more than the others. At an early stage of development branches extend from its right and left limbs toward the lungs (Figs 392, D, E, 393). After these pulmonary vessels have been established,² the right side of the sixth aortic arch loses communication with the dorsal aortic root and

² The details of the formation of the pulmonary arteries differ somewhat in different mammals. In most of the forms which have been carefully studied (*man, cat, dog, sheep, cow, opossum*) the pulmonary arteries maintain their original paired condition throughout their entire length. In these forms part of the right sixth arch is retained as the proximal portion of the adult right pulmonary artery. The pig is unusual in having its pulmonary branches fuse with each other proximally, forming a median vessel ventral to the trachea. Distal to this short median trunk the pulmonary vessels retain their original paired condition, each running to the lung on its own side of the body.

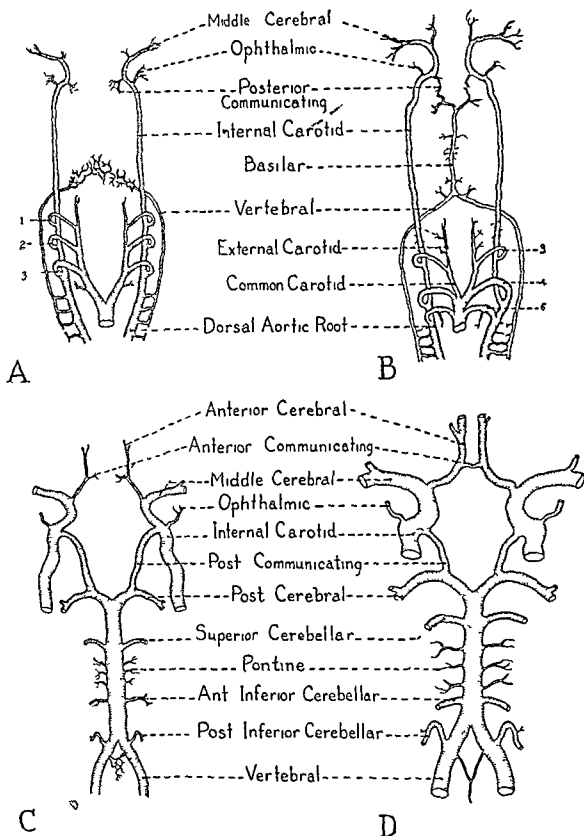


FIG 394 Schematic diagrams showing four stages in development of circle of Willis A, Plan of conditions in embryos of about 4 mm (Cf Fig 392, C) B, Conditions in embryos of about 6-8 mm (Cf Fig 392, D) C, Conditions in embryos of 20-25 mm (Cf Fig 392, F) D, Adult plan

disappears (Fig 393, B, C) On the left, however, the sixth arch retains its communication with the dorsal aortic root The portion of it between the point where the pulmonary trunk is given off and the dorsal aorta is called the ductus arteriosus (Figs 392, 393, 435) During the fetal period when the lungs are not inflated the ductus arteriosus shunts the excess blood from the pulmonary circulation directly into the aorta The functional importance of this channel will be more fully appreciated when it is again considered in connection with the development of the heart and the changes which take place in the circulation at the time of birth

SPLITTING OF THE TRUNCUS ARTERIOSUS While these changes have been taking place in the vascular channels which lead to the lungs, a fundamental alteration has occurred in the main ventral aortic stem Originally a single channel leading away from the undivided ventricle of the primitive tubular heart, the ventral aorta now becomes divided lengthwise into two separate channels This division begins in the aortic root just where the sixth arches come off, and progresses thence toward the heart Meanwhile, as we shall see, when we take up the development of the heart, the ventricle becomes divided into right and left chambers The final result of these two synchronous partitionings is the establishment of a pulmonary channel leading from the right ventricle to the lungs by way of the sixth aortic arches, and a separate ascending aortic channel leading from the left ventricle to the dorsal aorta by way of the left fourth aortic arch

Basilar and Vertebral Arteries There arise from the dorsal aortae a series of small paired vessels extending dorsally on either side of the neural tube Because they come off at regular intervals into the loose mesenchymal tissue between somites, these vessels are called the *dorsal intersegmental arteries* (Fig 396) In the cervical region the dorsal intersegmentals of either side early become joined by a series of anastomoses to form longitudinal channels parallel to the dorsal aortic roots (Figs 392, D, E, 393, B) These new paired longitudinal vessels, which become the vertebral arteries, grow cephalad and at the level of the developing medulla swing mesially and ventrally to join each other and form a median vessel, ventral to the developing brain This median vessel, the basilar artery, continues to grow rostrad to the level of the infundibulum where it is met by recurrent branches of the internal carotid arteries which, even at this early stage, can be recognized as constituting the posterior communicating arteries of the arterial circle of Willis (Figs 392, F, 394) The anterior communicating artery which forms between the anterior cerebral arteries to complete the circle appears at a considerably later time

While these changes have been occurring in the cephalic part of the system other related changes have been going on more caudally The arm buds have developed at the level of the sixth, seventh, and eighth intersegmental arteries, and one of these vessels, usually the seventh, extends into the upper extremity and, as the arm develops, becomes enlarged to form the subclavian artery (Fig 392, D, E) Gradually the intersegmental arteries which originally connected the dorsal aortic roots with the vertebral arteries drop out cephalic

to the subclavian (Fig 392, F) This leaves the vertebral arteries arising from the subclavians as they are found in the adult (Figs 393, C, 395)

Arteries of the Body-wall Caudal to the levels at which they are involved in the formation of the vertebral arteries, the dorsal intersegmental arteries of

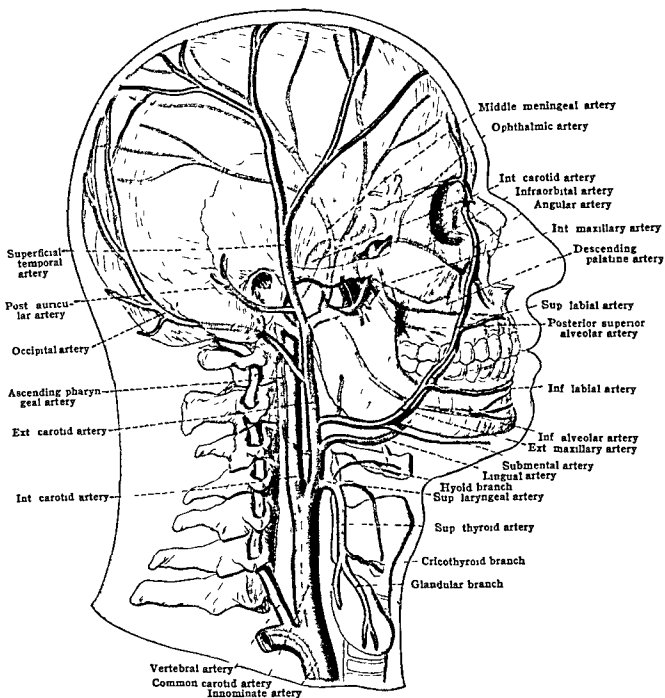


FIG 395 General relations of major branches of carotid arteries in adult (From Morris "Human Anatomy," after Tandler) The skull is represented as semitransparent to show the position of some of the deeper vessels

the embryo are retained in the adult in an arrangement that is basically similar to the primitive pattern. These vessels arise from the dorsal aorta while it is still in its primitive paired condition (Fig 396, A) and retain their own paired arrangement after the two aortae have fused to form a single main trunk (Fig 396, B, C). Originally associated primarily with the neural tube, as surround-

ing body-wall structures grow they send out new somatic branches. Gradually the branches which extend around the body-wall between the ribs become the most conspicuous, and for that reason the entire main vessel in the adult is called the intercostal. The early relations of these arteries to the neural tube are, however, still clearly indicated in the adult by their spinal branches (Fig 396, D)

Eventually the distal ends of the somatic branches of the original intersegmental arteries extend to the ventral body-wall as the intercostals at thoracic

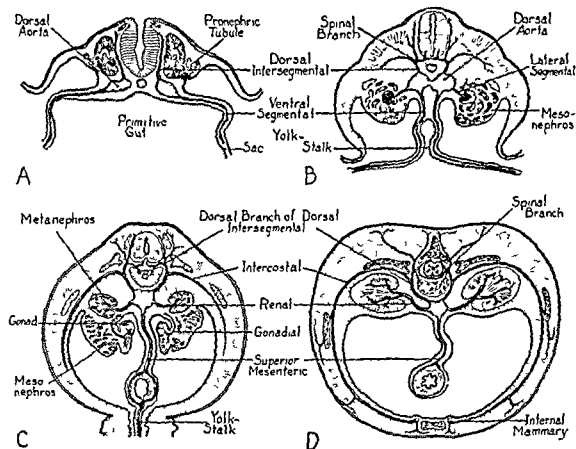


FIG 396 Cross sectional plans of the body showing relations of segmental branches of aorta at different stages of development

levels, and as the lumbar segmentals more caudally (Fig 397) Series of anastomoses join them to form a longitudinal channel on either side of the mid-line (Fig 396, D) At thoracic levels the new longitudinal vessel is known as the internal mammary artery, more caudally it is continued as the inferior epigastric artery (Fig 397)

The first two intercostal arteries usually form precostal anastomoses with each other and with the subclavian, close to their origin from the aorta With the disappearance of the proximal portions of the original intersegmentals the new anastomotic channel, known as the superior intercostal artery, feeds the first two intercostals from the subclavian Other than this slight modification effected by changes closely similar to those involved in the formation of the

vertebral artery, the basic embryonic arrangement of the dorsal intersegmentals persists in the adult

Arteries to the Viscera In addition to the dorsal intersegmental arteries there arise from the aorta two other series of paired arteries, one of which extends laterally and the other ventrally. The lateral vessels, although they

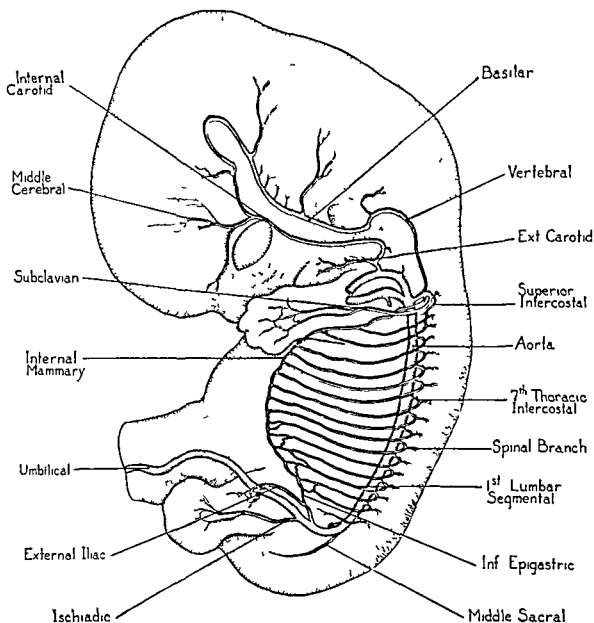


FIG 397 Arteries of the body wall in a human embryo of seven weeks (Modified after Mall)

arise very irregularly as far as their relations to somites are concerned, are commonly spoken of as the *lateral segmentals*. They are primarily associated with the internal urogenital organs. In young embryos their terminal branches form the glomeruli of the mesonephric tubules (Fig 396, B). At the height of the development of the mesonephros there are likely to be upward of 20 pairs of these vessels arising from the aorta at thoracic and lumbar levels. With the regression of the mesonephros practically all of these original vessels disappear except the arteries which become associated with the gonads (See artery

entering gonad by way of mesonephros, Fig 396, C) The manner in which the adult ovarian or internal spermatic arteries extend far caudad from an aortic origin near the renal level records the shift in position undergone by

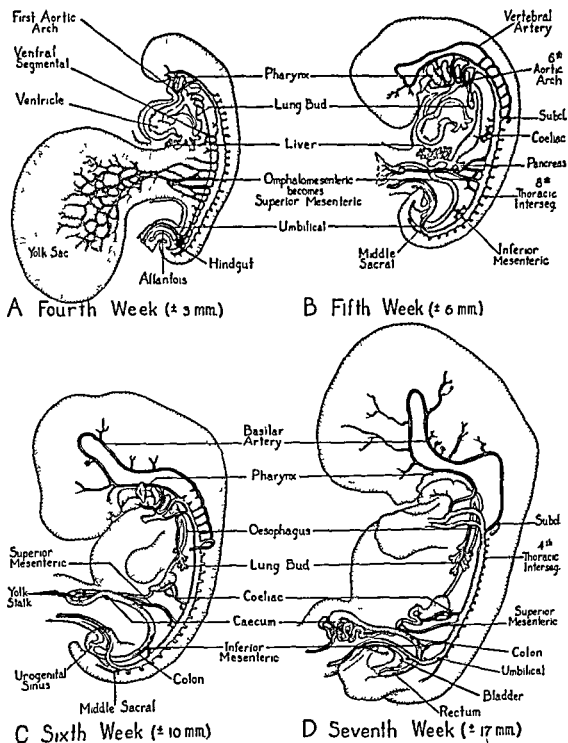


FIG 398 Development of coeliac and superior and inferior mesenteric arteries (Adapted from a number of sources)

the gonads subsequent to the time they acquired their vascular supply. Like the arteries to the gonads, the large arteries to the permanent kidneys (Fig 396, D) and the smaller arteries to the adrenals should be regarded as belong-

ing to this lateral series, although they do not become conspicuous until a later stage of development when most of the original lateral branches to the mesonephros have begun to disappear

The ventral series of vessels from the aorta is primarily associated with the

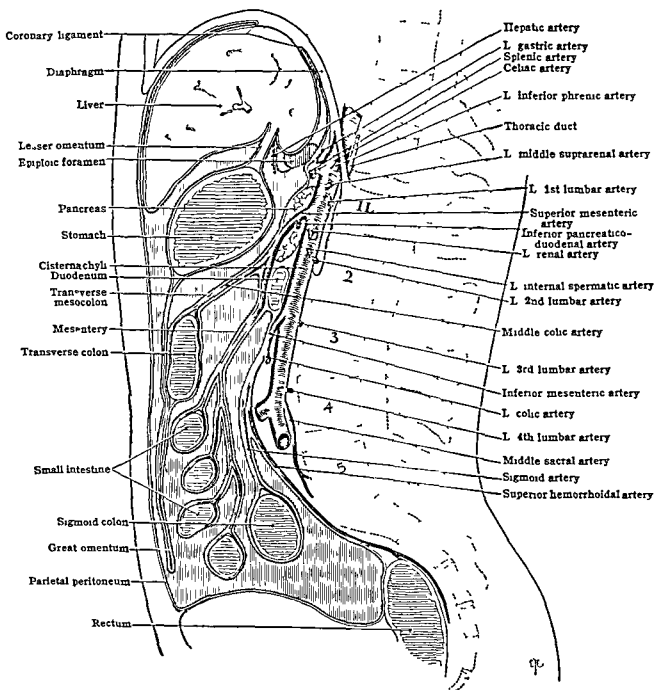


FIG. 399 Mesial plan of abdominal region to show distribution, in adult, of celiac and superior and inferior mesenteric arteries (From Morris "Human Anatomy")

yolk-sac and gut tract. As was the case with the lateral series these ventral vessels are commonly referred to as *ventral segmental arteries* in spite of considerable irregularity in their manner of origin. Like the more regularly arranged dorsal intersegmentals, the ventral segmental arteries arise at a very early stage of development when the aorta is still paired. In young embryos they

extend laterally over the dorsal wall of the primitive gut and thence peripherally into the walls of the yolk-sac (Fig 396, A) They constitute the arterial part of the omphalomesenteric arc of the embryonic circulation Later, as the intra-embryonic gut is delimited from yolk-sac and becomes supported by a mesentery, the right and left members of any particular pair of these ventral segmental vessels are brought close to each other (Fig 396, B) Eventually the two members of the pair fuse to form a median vessel lying in the mesentery (Fig 396, C, D) The three major arteries which arise ventrally from the adult aorta and supply the gut tract originate in this manner from the primitive ventral segmental branches They are the *celiac artery*, the *superior mesenteric artery*, and the *inferior mesenteric artery* (Fig 399) In the early developmental stages of these vessels there is a striking shift caudad in the points at which they originate from the aorta This accompanies the progressively more caudal position assumed by the viscera during this period The change in the points of origin of the enteric arteries from the aorta depends, especially during the early stages of the process, on the free anastomosis between the ventral segmentals at different levels (Fig 398, A, B) This permits the dropping out of the more cephalic roots and the utilization of the more caudal ones, without interruption of circulation, as the change in visceral position progresses Later in development after the celiac, superior, and inferior mesenteric arteries have been established as main vessels, there appears to be some further shift caudad due to differential growth about their point of origin from the aorta Toward the close of the second month of development all these vessels have attained approximately their adult level of origin (cf Figs 398, D, 399)

Umbilical Arteries The umbilical arteries to the placenta should be regarded as belonging originally to the ventral segmental series They arise at the caudal end of the aorta in association with the allantoic diverticulum of the hindgut (Fig 74) Unlike the celiac and mesenteric arteries they maintain their original paired condition (Fig 435) With the rapid growth of the caudal end of the young embryo there is some tailward shift in the position of origin of the umbilical arteries from the aorta This is accomplished in a manner similar to that described above for the celiac and mesenteric arteries, but the change in position is by no means as extensive as it is in the case of the arteries to the gut tract

Arteries of the Extremities The origin of the proximal part of the subclavian artery has already been discussed in dealing with the changes in the aortic arches and with the origin of the vertebral arteries In the later stages of development an interesting change in the relation of the left subclavian occurs The original point of origin of the seventh intersegmental, which becomes enlarged to form the subclavian, is well caudal to the level at which the ductus arteriosus joins the descending part of the arch of the aorta (Fig 392, D-F) But during development the heart moves caudad in the body from the site of its origin, carrying with it the associated great vessels This change in cardiac position is recorded in the downward course of the cardiac nerves which first attained their relations to the heart when it lay opposite the body

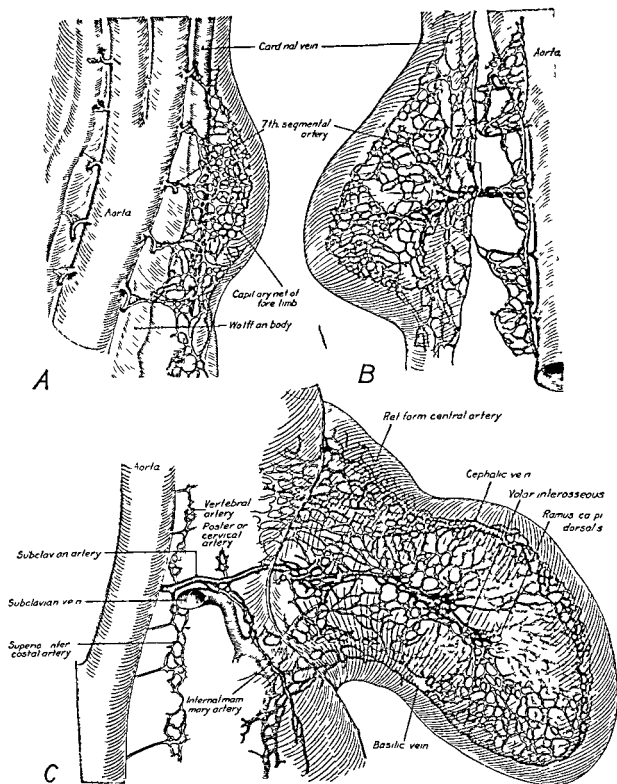
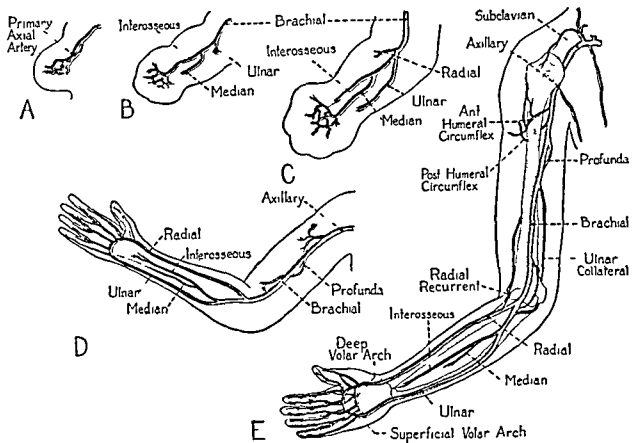


FIG. 400 Drawings from injected pig embryos showing three stages in early development of blood vessels of anterior appendage bud (After Woollard, Carnegie Cont. to Emb., Vol. 14, 1922.) A, Embryo of 4.5 mm (equivalent to four-week human embryo) B, Embryo of 7.5 mm (equivalent to five-week human embryo) C, Embryo of 12 mm (equivalent to six-week human embryo)

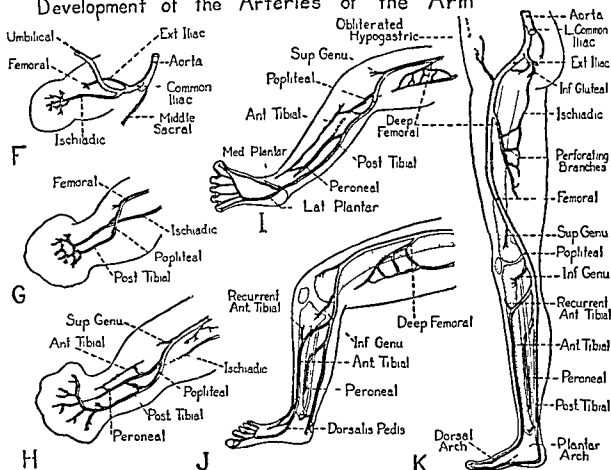
extend laterally over the dorsal wall of the primitive gut and thence peripherally into the walls of the yolk-sac (Fig 396, A) They constitute the arterial part of the omphalomesenteric arc of the embryonic circulation Later, as the intra-embryonic gut is delimited from yolk-sac and becomes supported by a mesentery, the right and left members of any particular pair of these ventral segmental vessels are brought close to each other (Fig 396, B) Eventually the two members of the pair fuse to form a median vessel lying in the mesentery (Fig 396, C, D) The three major arteries which arise ventrally from the adult aorta and supply the gut tract originate in this manner from the primitive ventral segmental branches They are the *celiac artery*, the *superior mesenteric artery*, and the *inferior mesenteric artery* (Fig 399) In the early developmental stages of these vessels there is a striking shift caudad in the points at which they originate from the aorta This accompanies the progressively more caudal position assumed by the viscera during this period The change in the points of origin of the enteric arteries from the aorta depends, especially during the early stages of the process, on the free anastomosis between the ventral segmentals at different levels (Fig 398, A, B) This permits the dropping out of the more cephalic roots and the utilization of the more caudal ones, without interruption of circulation, as the change in visceral position progresses Later in development after the celiac, superior, and inferior mesenteric arteries have been established as main vessels, there appears to be some further shift caudad due to differential growth about their point of origin from the aorta Toward the close of the second month of development all these vessels have attained approximately their adult level of origin (cf Figs 398, D, 399)

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Development of the Arteries of the Arm



Development of the Arteries of the Leg

FIG. 401 Development of arteries of extremities (Based, in part, on the work of Senior)

segments from which the vagus and cervical sympathetic fibers arose. The left subclavian artery, however, appears to maintain a relatively more direct course, by the gradual upward migration of its origin from the primary site well below the entrance of the ductus arteriosus (Figs 392, F, 393, C), to a definitive origin from the aortic arch above the ligamentum arteriosum (See arrow in Fig 393, C). There still remains, however, a definite ascending course in the proximal part of the subclavian (Fig 402) which is a partial record of the caudal movement of the heart and aorta during their development. In the light of this developmental history, considerable variability of the position in which the adult left subclavian artery arises from the aorta becomes readily understandable.

The manner in which the main arterial branches in the appendages develop is schematically summarized in Fig 401. The primary artery to the arm is axial in position (Fig 400, C). Proximally it becomes the main subclavian-axillary-brachial trunk, below the elbow it persists in reduced form as the interosseus (Fig 401, E). The primordial plexus of vessels in the developing hand is fed first by the original axial artery. A parallel branch—the median artery—then for a time takes over the supply of this plexus with which the original axial connection is lost (Fig 401, C). A little later the ulnar, and then the radial, arteries develop as parallel branches of the primordial axial artery, and serve as the final vessels supplying the arm and connecting with the deep and superficial volar arches formed from the primary plexus of small vessels in the developing hand. The deep (*profunda*) branch of the brachial artery and the smaller branches to the shoulder and elbow develop at a relatively late stage as new offshoots of the primary axial vessel (Fig 401, D, E).

The posterior appendage buds arise some time after the placental circulation has been established. The umbilical arteries are consequently of considerable size, and the small vessels which branch off from them to feed the appendage buds are by comparison quite insignificant (Fig 401, F). As was the case with the arm, the primary artery of the leg is axial in position. It arises from the umbilical artery where that vessel passes close to the root of the developing limb bud. It is called the ischiadic artery, or sometimes simply the "axis artery." The ischiadic artery later disappears as a main channel, a portion of the peroneal and the inferior genu, a small descending branch of the inferior gluteal, and the longitudinal anastomotic vessels connecting the branches of the deep femoral artery being its only remains (Fig 401, H-K). The external iliac artery, which arises from the umbilical somewhat proximal to the ischiadic, soon becomes the main arterial route to the leg. It is prolonged distally under different names at different levels, being called successively femoral, popliteal, and posterior tibial. Where, in its popliteal portion, it passes close to the ischiadic, an anastomosis is formed so the lower part of the ischiadic, reduced in relative size, becomes the peroneal (Fig 401, H-K).

The anterior tibial artery is a new channel parallel to the posterior tibial and the peroneal. It is formed by

ing small branches extending from the primary axial artery toward the anterior surface of the leg (Fig 401, H, I) With the formation of a new anastomosis connecting the anterior tibial with the posterior tibial, the original branches from the regressing axial trunk disappear and the anterior tibial appears as a branch of the posterior (Fig 401, I, J)

The primordial vascular plexus in the foot is originally fed by the primary axial (ischadic) artery (Fig 401, F) Early in development this connection regresses as the foot plexus is taken over by the posterior tibial extension of the external iliac-femoral trunk (Fig 401, G, H) Later the newly formed anterior tibial artery also makes connection with the developing vessels of the foot As the dorsal and plantar vessels of the foot take shape, the anterior tibial comes to supply the dorsal arcuate artery and its branches while the posterior tibial supplies the plantar vessels

When, at birth, the placental circulation stops, the umbilical arteries are reduced to small vessels nourishing local tissues between their point of origin and the umbilicus We then know their proximal portions as the internal iliac, or hypogastric, arteries and the fibrous cords which still mark their course along the wall of the bladder (the old allantoic stalk) as their "obliterated branches"

Thus the tables are turned between fetal and adult life In the fetus the external iliac artery to the leg appears as a branch of the dominating umbilical artery After birth the reduced umbilical arteries under their new name of hypogastrics appear as branches of the now larger external iliacs The original umbilical root proximal to the origin of the external iliac is called the common iliac (Figs 435, 446)

VEINS

There is a natural grouping of the veins according to their relationships which it is convenient to follow in discussing their development Under the term systemic veins we can include all the vessels which collect the blood distributed to various parts of the body in the routine of *local metabolism* In young embryos these would be the cardinal veins and their tributaries—that is to say, the return channels of the primitive intra-embryonic circulatory arc In older embryos and adults the systemic veins would include the superior caval system which is evolved from the anterior cardinals, and the inferior caval system which takes the place of the postcardinals and their tributaries

We can set apart from the general systemic circulation three special venous arcs (1) The umbilical, returning the blood from the placenta, (2) the pulmonary, returning the blood from the lungs, and (3) the hepatic-portal, carrying blood from the intestinal tract to the liver The specialized nature of the placental and pulmonary circulations is obvious The peculiarities of the hepatic portal system call, perhaps, for a word of explanation Ordinarily veins³ collect blood from local capillaries and pass it on directly to the heart

³ There is a tendency among those who have done but little work on the circulation to regard any vessel which carries oxygenated blood as an artery and any vessel which carries blood poor in

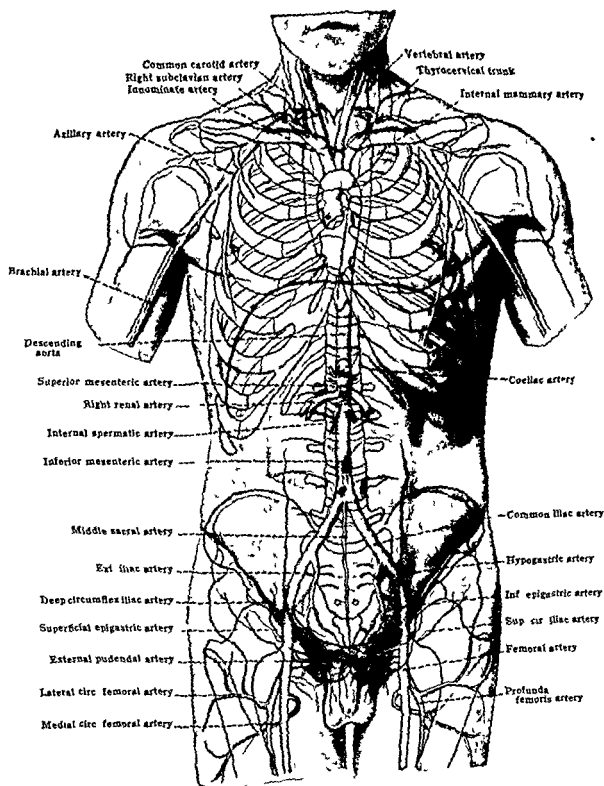


FIG 402 General plan of main arteries of adult body (From Morris "Human Anatomy," after Tandler)

During the succeeding stages of development (Fig 404, E, F) the *inferior petrosal sinus* appears and the sagittal plexus becomes differentiated into the *superior and inferior sagittal sinuses* and *sinus rectus* (Fig 405) The tentorial plexus becomes the *confluens sinuum* and the horizontal part of the transverse sinuses

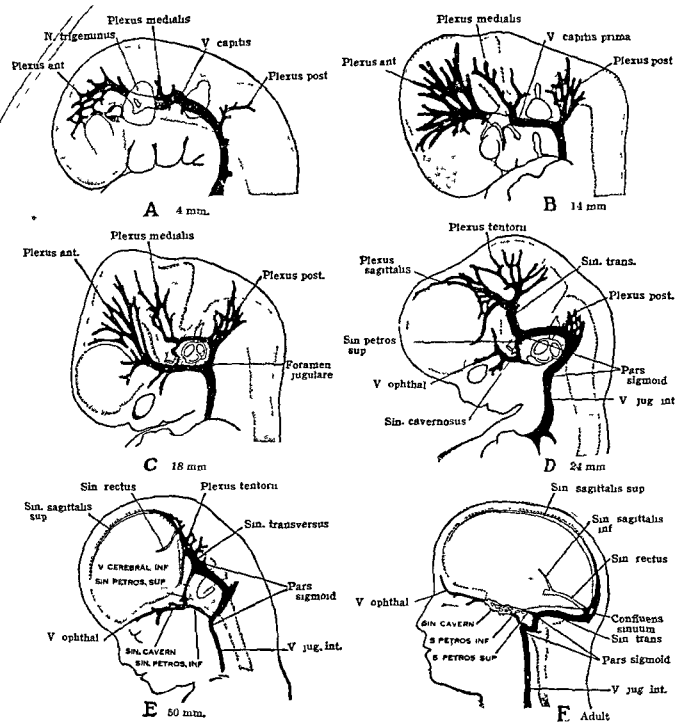


FIG 404 Stages in development of dural venous sinuses (After Streeter, Carnegie Cont to Emb, Vol 7, 1918)

Its connections with the posterior dural plexus form the *sinus occipitalis*, and the plexus itself persists, in part, as the *marginal sinuses*. The great variability of the pattern encountered in the dural sinuses of the adult is readily understandable in the light of the freely anastomosing relations of the embryonic venous channels from which they develop.

(Fig 403, A, B), eventually are drained into the anterior cardinals (Fig 403, C, D)

In the anterior systemic channels the shift of the venous flow to enter the heart on the right is accomplished very simply and directly. A new vessel forms between the right and left anterior cardinals by confluence and anastomosis of the small thymico-thyroid veins. Through this channel the left cardinal blood stream is shunted across to the right (Fig 403, D). With the establishment of this new channel, the part of the left anterior cardinal toward the heart drops out (Fig 403, E) and we have now but to apply the familiar adult names (Fig 403, F). The new connecting vessel is the *left innominate*, the old right anterior cardinal between the union of the subclavian with the jugulars and the new transverse connection is the *right innominate*, from the confluence of the innominates to the heart is the *superior vena cava*. The superior vena cava is thus composed of the most proximal part of the right anterior cardinal and the right common cardinal vein. The place of entrance of the azygos vein (the reduced right posterior cardinal) indicates the old point of transition from anterior cardinal to common cardinal. The external and the anterior jugular veins appear relatively late in development by the gradual organization of small vessels which were tributaries of the anterior cardinals at cervical levels.

The cephalic portions of the anterior cardinals originally arise in intimate association with the developing brain and become modified to form the drainage channels of the adult head. The part of the anterior cardinal into which the tributary veins from the different regions of the embryonic brain converge is called the *vena capitis prima* (Fig 404, B). With the growth of the investing layers about the brain the venous plexuses draining into the *vena capitis prima* become differentiated into vessels which drain the dura, in addition to the original deeper vessels associated with the brain. In the later stages of development the main tributaries are those which lie in the dura mater. On this account, to designate the three main sets of tributaries discharging into the *vena capitis prima*, the terms *anterior*, *middle*, and *posterior dural plexus* have been substituted by Streeter for the older terms *anterior*, *middle*, and *posterior cerebral veins*.

Toward the close of the second month of development a new connection arises between the middle and posterior dural plexuses (Fig 404, C). This, together with the stem of the posterior plexus, will become the *sigmoid part of the sinus transversus*. A little later the anterior and middle dural plexuses coalesce to form the sagittal and tentorial plexuses (Fig 404, D). The part of the *vena capitis prima* upon the medial side of the trigeminal ganglion can now properly be called the *sinus cavernosus*. It receives the ophthalmic and middle cerebral veins (Fig 404, D). The remainder of the *vena capitis prima* undergoes regressive changes and the blood from the cavernous sinus drains into the *transverse sinus* through the *sinus petrosus superior*—originally the lower part of the stem of the middle plexus (Fig 404, C, D). The drainage of all the venous channels in the dura mater is now effected through the *sinus transversus*.

them. The inferior vena cava which replaces the cardinals is a composite vessel which gradually takes shape by the enlargement and straightening of originally small local channels which are, as it were, pressed into service as the posterior cardinals degenerate.

The *subcardinal veins* initiate the diversion of the postcardinal blood stream. The subcardinals are established as vessels lying along the ventromesial borders of the mesonephroi parallel with, and ventral to, the postcardinals (Fig 403, A, B, G). Taking origin from an irregular plexus of small vessels emptying from the mesonephroi into the posterior cardinals, the subcardinals, from their first appearance, have many channels connecting them with the postcardinals (Fig 403, A). As the mesonephroi increase in size and bulge toward the midline, the subcardinals are brought very close together. In the mid-mesonephric region they establish communication with each other by several small vessels which soon become confluent to form a conspicuous *intersubcardinal anastomosis* (Fig 403, B-D, H). As the anastomosis increases in size, it, together with the subcardinals where they are thus joined, forms a large medial venous space called the *subcardinal sinus*. When this sinus is established, the small vessels connecting sub- and postcardinals drain medially into it rather than laterally toward the posterior cardinals. The result of this change very soon becomes apparent in the disappearance of the posterior cardinals at the level of this sinus (Fig 403, C). The blood from the posterior part of the body is still collected by the distal ends of the postcardinals but it returns to the heart by way of the subcardinal sinus. Consequently, the anterior portions of the posterior cardinals although they do not disappear entirely become much reduced in size (Fig 403, C, D).

Meanwhile the increased volume of blood entering the subcardinal sinus is finding a new and more direct route to the heart. The cephalic pole of the right mesonephros lies close to the liver, and a fold of dorsal body-wall tissue, just to the right of the primary dorsal mesentery, early makes a sort of bridge between these two organs. This fold is known as the caval plica or caval fold of the mesentery (Fig 302). In it, as everywhere in the growing body, are numerous small vessels. Connection of these small vessels with the plexus of channels in the liver cephalically, and the mesonephros caudally, provides the entering wedge. Once a current of blood finds its way from the mesonephros to the liver through these small vessels, enlargement of the channel proceeds with great rapidity. This new channel becomes the *mesenteric part of the inferior vena cava* (indicated by small crosses in the diagrams of Fig 403).

Within the liver this new blood stream at first follows devious small channels, eventually entering the sinus venosus along with the omphalomesenteric circulation (Fig 403, B). As its volume of blood increases it excavates through the liver a main channel which gradually becomes walled in. As this new vessel becomes more and more definitely organized it gradually crowds toward the surface and eventually appears as a great vein lying in a notch along the dorsal side of the liver. This is the *hepatic part of the inferior vena cava*. From the subcardinal sinus the most direct route to this new outlet is by way of the

The veins of the upper extremity at first are merely part of the general superficial venous plexus of the neck and thorax, which is drained by the cardinal veins. Upon the free border of the developing limb (Fig 400) a marginal vein soon becomes apparent, the preaxial and postaxial limbs of which are known as the cephalic vein and the basilic vein, respectively. The drainage of the upper extremity and the chest is later taken over by the sub-

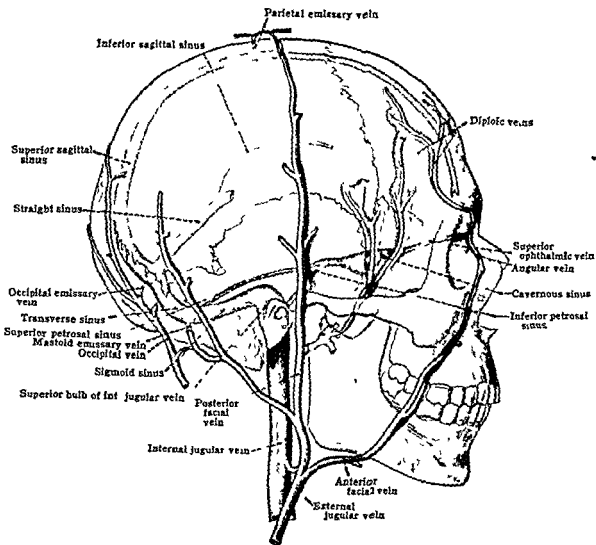


FIG 405 Semischematic drawing to show relations of intra- and extracranial veins (From Morris "Human Anatomy," after Tandler)

clavian vein, a gradually enlarging channel which connects the basilic vein with the anterior cardinal. The developing subclavian vein receives the largest vein of the embryonic chest, the thoraco-epigastric, which persists in the adult as the *lateral thoracic vein*.

INFERIOR CAVAL SYSTEM The changes in the systemic veins of the posterior part of the body are much more radical than they are anteriorly. The posterior cardinal veins, which are the primitive systemic drainage channels, are associated primarily with the mesonephroi. When the mesonephroi degenerate, it is but natural that the posterior cardinals should degenerate with

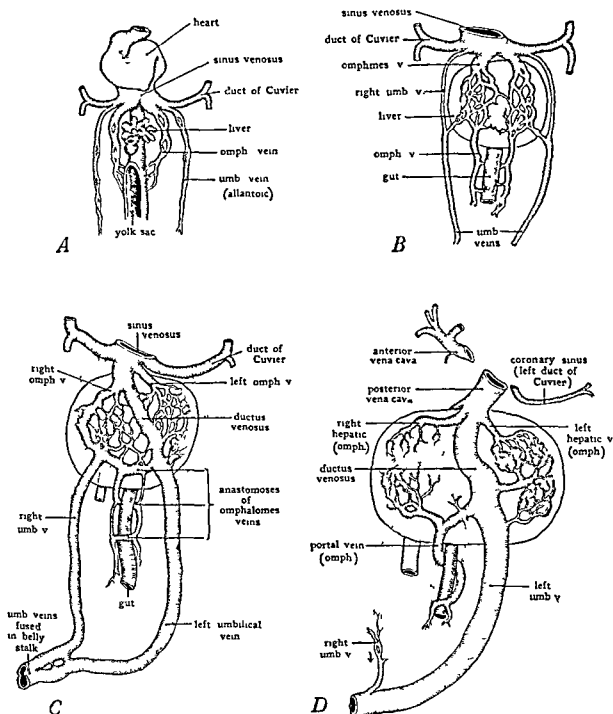


FIG. 406 Diagrams showing development of hepatic portal circulation from omphalomesenteric veins, and changes by which blood returning from placenta by way of umbilical veins is rerouted through liver. A, Based on conditions in pig embryos of 3-4 mm—applicable to human embryos of fourth week. B, Based on pig embryos of about 6 mm—applicable to human embryos of fifth week. C, Based on pig embryos of 8-9 mm—applicable to human embryos early in sixth week. D, Based on pig embryos of 20 mm and above—applicable to human embryos of seven weeks and older.

right subcardinal vein. Thus in embryos as young as six weeks (Fig 403, C) the formation of the inferior vena cava is well started with its prerenal portion consisting of subcardinal sinus, a portion of the right subcardinal vein, and the new channels through the mesentery and through the liver.

Posterior to the level of the subcardinal sinus—which is at the future renal level—still another set of veins enters into the formation of the inferior vena cava. These are the *supracardinal veins* which appear, later than the subcardinals, as paired channels draining the dorsal body-wall (Fig 403, I). At mid-mesonephric level, the supracardinals make connection with the subcardinal sinus just as happened with the postcardinals earlier in development. Cephalic to the sinus, parts of the supracardinals persist as the azygos group (Figs 407, 408) draining in a somewhat variable manner into the reduced proximal part of the right postcardinal. Caudal to the anastomosis with the subcardinal sinus, the supracardinals become the principal return route from the veins draining the pelvis and legs (Fig 403, D). With the formation of an anastomosis connecting the right and left iliacs, the blood returns increasingly by way of the right supracardinal which gradually becomes enlarged to form the *postrenal portion of the inferior vena cava* (Fig 403, D, E). The manner in which the adult vena cava caudal to the renal level swings to a more dorsal position with reference to the aorta clearly indicates its origin from the more dorsally located right supracardinal rather than from the more ventrally located right postcardinal as was formerly supposed. The course of the adult left suprarenal and left gonadal vein (Fig 403, E, F) chronicles in an interesting manner their origin from parts of the old left subcardinal vein.

Coronary Sinus The ultimate fate of the left common cardinal vein (duct of Cuvier) is a result of the shift in the course of the systemic blood so that it all enters the right side of the heart. Formerly returning a full half of the systemic blood stream to the heart, the left common cardinal vein is finally left almost without a tributary from the body. Nevertheless, the proximal part of the old left cardinal channel is utilized. Pulled around the heart in the course of the migration of the sinus venosus toward the right, the left duct of Cuvier lies in the atrioventricular sulcus close against the dorsal wall of the heart for a considerable distance (Fig 417, C-E). As the heart muscle grows in bulk it demands a greater blood supply for its metabolism. The small returning veins of this circulation find their way into this conveniently located main vessel (Fig 417, E, F). Thus, even when its peripheral circulation is cut off, the proximal part of the left duct of Cuvier still persists as the coronary sinus into which the veins of the cardiac wall drain.

Pulmonary Veins Phylogenetically, the lungs are relatively new structures. It is not surprising, therefore, that we find the pulmonary veins arising independently and not by the conversion of old vascular channels. They originate as vessels which drain the various branches of the lung buds and converge into a common trunk entering the left atrium dorsally (Fig 417, D). In the growth of the heart this trunk vessel is gradually absorbed into the atrial wall until usually four of its original branches come to open directly into

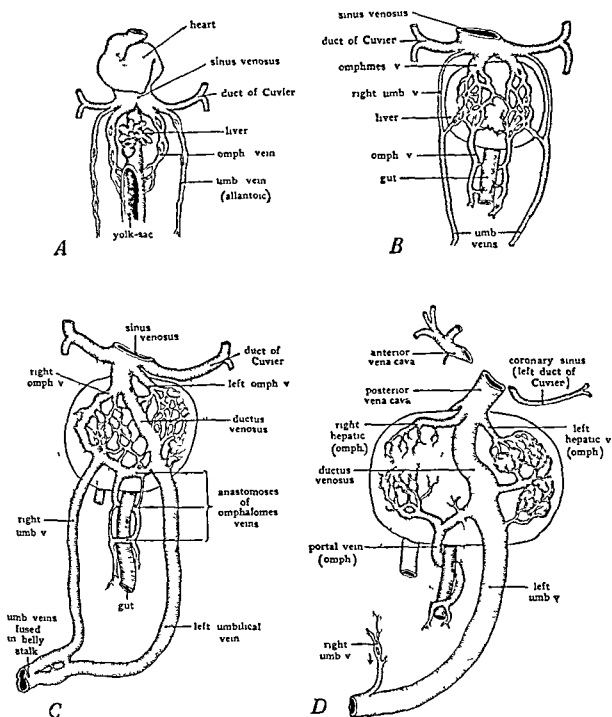


FIG 406 Diagrams showing development of hepatic portal circulation from omphalomesenteric veins, and changes by which blood returning from placenta by way of umbilical veins is rerouted through liver A, Based on conditions in pig embryos of 3-4 mm—applicable to human embryos of fourth week B, Based on pig embryos of about 6 mm—applicable to human embryos of fifth week C, Based on pig embryos of 8-9 mm—applicable to human embryos early in sixth week D, Based on pig embryos of 20 mm and above—applicable to human embryos of seven weeks and older

the left atrium as the main pulmonary veins of the adult (Fig 417, E, F) Less than the usual amount of resorption of the primitive common pulmonary vein not infrequently results in the pulmonary veins from the right and left lungs entering the left atrium as single instead of the usual paired vessels

Portal Vein The primitive blood supply to the gastro-intestinal tract is from the series of ventral segmental arteries which ramify in the walls of the primitive gut and yolk-sac and ultimately become modified into the celiac, and the superior and inferior mesenteric arteries (Fig 398) The venous return of this primitive gut circulation is originally by the way of the vitelline veins of the yolk-sac which become confluent as the main paired omphalomesenteric veins and enter the sinus venosus posteriorly (Figs 392, A-C, 406, A) As they approach the heart these veins skirt the margins of the anterior intestinal portal and thus lie adjacent to the developing liver The growing cords of hepatic tissue break up the proximal portion of the omphalomesenteric veins into a maze of small channels ramifying through the substance of the liver (Figs 392, D, 406, B), but the stubs of the omphalomesenterics persist and drain this plexus Distal to the liver, the original veins are for a time retained, bringing blood from the yolk-sac and intestines to the liver With the disappearance of the yolk-sac and the growth of the intestines, the omphalic (yolk-sac) portions of these veins necessarily disappear, but the mesenteric branches persist and become more extensive, concomitantly with the increased length and complexity of the intestinal tract (Fig 407)

The original omphalomesenteric trunks into which these tributaries converge become the unpaired portal vein by forming transverse anastomoses and then abandoning one of the original channels The curious spiral course of the portal vein is due to the dropping out of the original left channel anterior to the middle anastomosis and the original right channel posterior to the anastomosis (Fig 406, D)

Umbilical Veins When they are first established, the umbilical (allantoic) veins are embedded in the lateral body-walls throughout their course from the belly-stalk to the sinus venosus (Fig 74) As the liver grows in bulk, it fuses with the lateral body-wall Where this fusion occurs, vessels develop connecting the umbilical veins with the plexus of vessels in the liver (Fig 406, B) Once these connections are established, the umbilical stream tends more and more to pass by way of them to the liver and the old channels to the sinus venosus gradually degenerate (Fig 406, C)

Meanwhile the umbilical veins distal to their entrance into the body become fused with each other so that there comes to be but a single vein in the umbilical cord (Fig 406, C) Following this fusion in the cord, the intra-embryonic part of the umbilical channel also loses its original paired condition The right umbilical vein is abandoned as a route to the liver and all the placental blood is returned by way of the left umbilical vein It is interesting to note that in spite of its ceasing to be a through channel, part of the right umbilical vein persists draining the body-wall The small blood stream it then carries is reversed in direction, flowing back into the left umbilical vein (Fig 406, D)

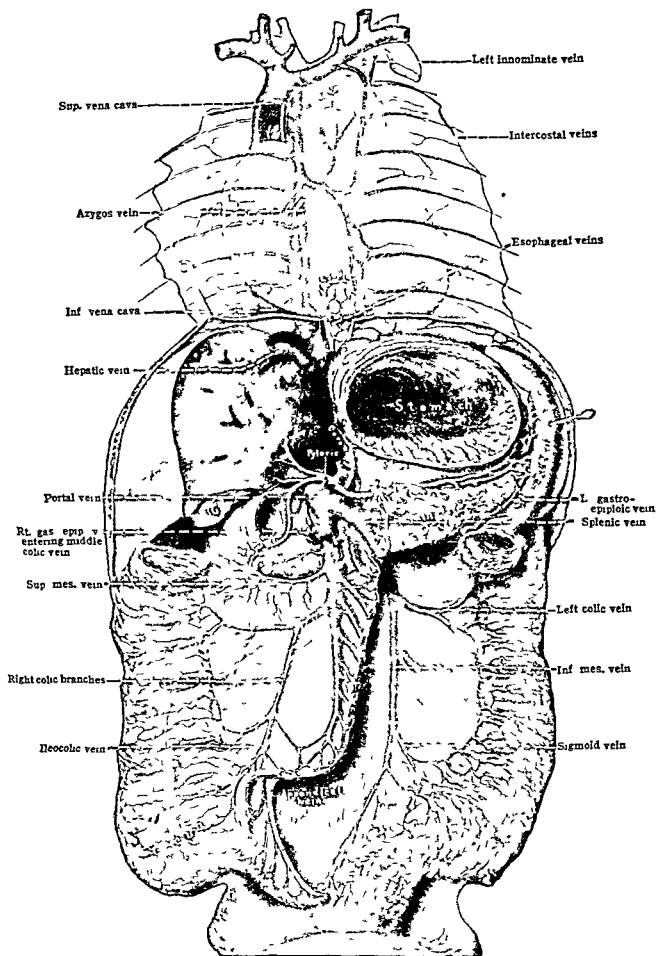


FIG. 407 Portal vein and its major tributaries as seen in a ventral dissection of an adult (From Morris "Human Anatomy," after Kelley)

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When first diverted into the liver, the umbilical blood stream passes through by way of a meshwork of small anastomosing sinusoids. As its volume increases it excavates a main channel through the substance of the liver which is known as the *ductus venosus* (Fig 406, B-D). Leaving the liver the ductus venosus is joined by the hepatic veins (omphalomesenteric stubs) which drain the maze of sinusoids in the liver. At this point, also, the vena cava becomes confluent with the hepatic veins and the ductus venosus. Thus the blood streams from the posterior systemic circulation, from the portal circulation, and from the placental circulation all enter the heart together. Embryologically, this great trunk vessel represents the fused proximal parts of the old omphalomesenteric veins enlarged by the placental blood from the ductus venosus and by the systemic blood from the vena cava (Figs 406, 446). In the adult (Fig 408) it is regarded as a part of the vena cava because, with the cessation of the placental circulation at the time of birth the caval blood stream is the dominant one.

DEVELOPMENT OF LYMPHATIC SYSTEM

Primordial Lymph Sacs The first indication in the embryo of the establishment of the lymphatic system becomes evident in the sixth week of development. In embryos of about 10 mm, paired (right and left) *jugular lymph sacs* can usually be recognized. These sacs are formed from small endothelially lined channels which are originally part of the primitive vascular plexus at cervical levels of the developing anterior cardinal veins (Fig 409). Some of these small channels lose their connection with the main vein and become temporarily blind sacs lying adjacent to the veins (Fig 409, B). During this period they are likely to contain trapped blood corpuscles which are again released into the circulation when these primitive lymphatic sacs become re-connected with the venous system. Although the period of re-establishing connection with the venous system shows considerable variability, the jugular lymph sacs usually reopen into the anterior cardinal veins toward the end of the sixth or early in the seventh week (embryos of from 12 to 14 mm).

During the seventh week there is considerable extension of the jugular lymph sacs by dilation of the original sacs themselves, and also by their coalescence with adjacent endothelial pockets. A little later other similar lymphatic sacs appear in the axillary and inguinal regions, along the dorsal body-wall in association with the azygos veins and the developing inferior vena cava, and at the roots of the mesenteries. The most conspicuous of these sacs can be named conveniently on the basis of their future relations. That in the axillary region is known as the *subclavian lymph sac*. The chain of small sacs along the dorsal body-wall constitutes the primordium of the main longitudinal lymphatic drainage channel of the body known as the *thoracic duct* (Figs 410, 411). Retroperitoneally, in the lumbar region, a large median sac is the forerunner of the *cisterna chyli* (Figs 411, 413). Developing in intimate association with the cisterna chyli, but ventral to it, is the *retroperitoneal lymph*

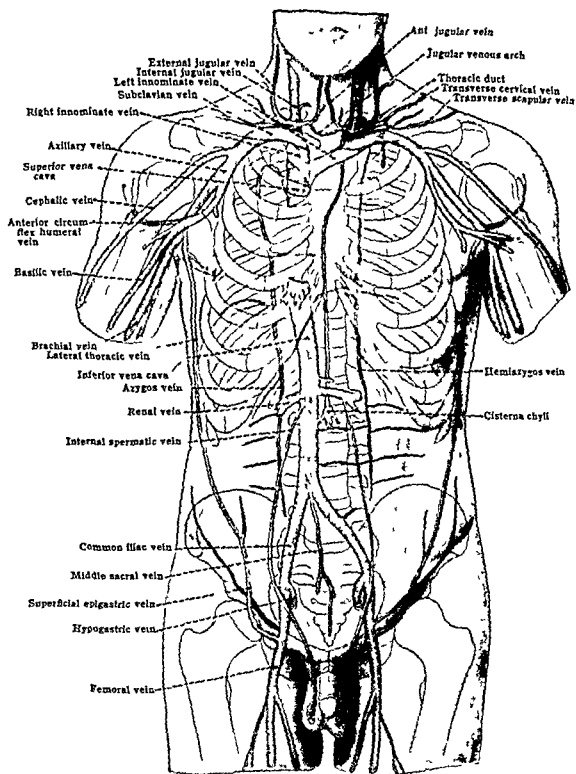


FIG 408 General plan of systemic veins of adult (From Morris "Human Anatomy," after Tandler)

channels which form free anastomoses with the retroperitoneal vessels in the region of the kidneys and the internal genitals

Establishing of the Major Lymphatic Channels By the ninth week the pattern of the main lymphatic channels has taken quite definite shape. The *thoracic duct* is now a continuous channel which, at its cephalic end, opens

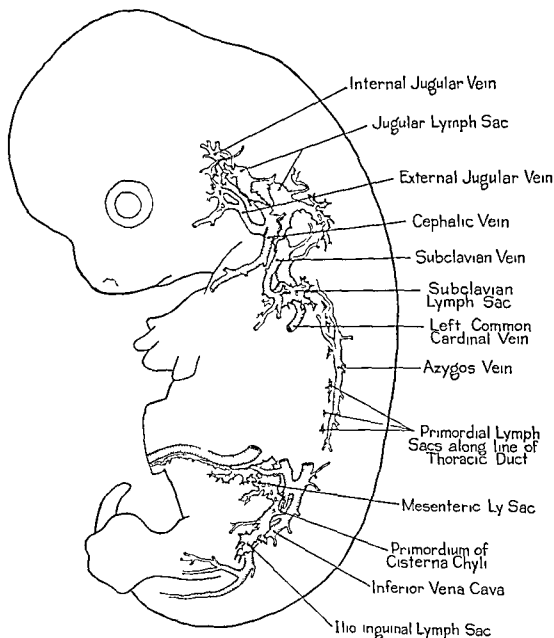


FIG 410 Lymphatic system of 15-mm cat embryo (Modified after F T Lewis, *Am J Anat*, Vol 5, 1906) This animal material supplies a valuable intermediate stage between Fig 409, a human embryo of the sixth week, and Fig 411, a human embryo at beginning of the ninth week.

freely into the jugular lymphatic sac on the left, giving clear indication of the way the *left jugular lymphatic trunk* and the thoracic duct are destined to open together into the left innominate vein near the angle of confluence of the jugular and subclavian veins. The *right jugular lymphatic trunk* ordinarily opens into the right innominate in a corresponding position. Where these main lymphatic channels open into the venous system there are well-developed

sac As extensions from this sac, lymphatic spouts grow into the mesenteries (See the mesenteric lymph sac in Fig 410) When these channels have developed they provide the lymphatic drainage of the gastro-intestinal tract except for the rectal region Also arising in association with this retroperitoneal sac is a plexus of vessels draining the renal and genital areas

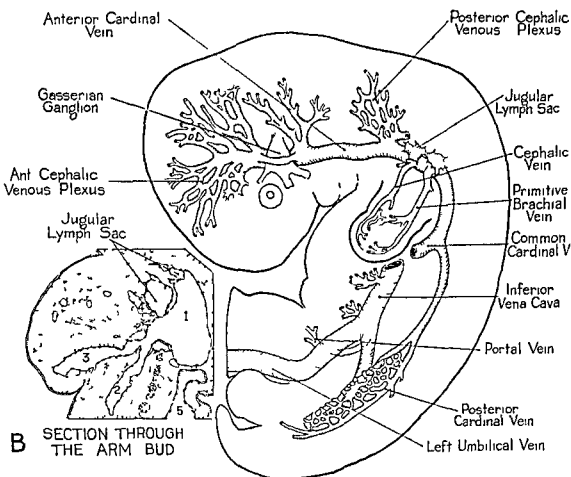


FIG 409 Diagram showing relations of jugular lymph sac to venous system in 10.5-mm human embryo (Redrawn after Sabin, in Keibel and Mall "Manual of Human Embryology," courtesy, J B Lippincott Co)

Insert, B, showing jugular sac in section is from an 11-mm human embryo
 Key 1, anterior cardinal vein (internal jugular vein), 2, lateral thoracic vein, 3, primitive brachial vein, 4, cephalic vein, 5, coelom

Arising as a caudal continuation of the cisterna chyli, at a level more dorsal than the retroperitoneal sac, are the paired *iliac sacs*. These primordial sacs show ilio-lumbar dilations at the renal level and ilio-inguinal expansions at about the level of the bifurcation of the aorta (Fig 413). The plexus of lymphatic channels arising in the dorsal body-wall between the kidneys comes to constitute the retrorenal drainage system of the adult. The ilio-inguinal sacs are extended along the course of the iliac vessels to the appendages. There are also important medial extensions from the ilio-inguinal sacs which come to drain the rectum and perineum (Fig 413). In addition there are

Growth of Peripheral Lymphatics The extension of the small channels from the primary sacs and channels takes place by the growth of *endothelial sprouts* which are at first solid and then, as they extend, become hollow to form lymphatic vessels. The nature of the processes involved in this growth has been very carefully studied by E. R. and E. L. Clark in living amphibian larvae, and their diagrams of this growth process, made from the same living specimen at intervals, give us a clear picture of the way this process undoubtedly goes on in human embryos (Fig 414). At the same time the smaller channels are being expanded peripherally, the lymphatic sacs are being

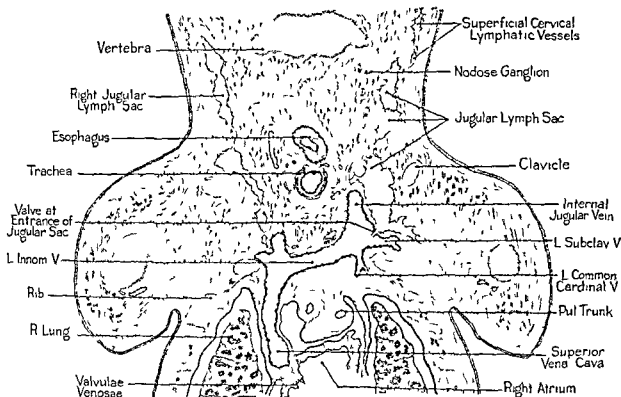


FIG 412 Frontal section of human embryo of 30-mm (beginning of ninth week) showing entrance of left jugular lymph sac into internal jugular vein (Redrawn after Sabin, in Keibel and Mall "Manual of Human Embryology," courtesy, J. B. Lippincott Co.)

molded into more restricted channels by the ingrowth of strands of connective tissue which break up the originally capacious lumina into main channels following along certain lines, and a series of small and delicate tributary channels continuous with the peripherally growing sprouts.

Formation of Lymph Nodes When the lymphatic vascular channels have been fairly well sketched out, lymph nodes begin to make their appearance in the system. The earliest of these nodes to take shape arise in connection with the jugular and ilio-inguinal lymph sacs in regions where they are being broken up by connective-tissue ingrowths. Certain of these areas of connective tissue are colonized by lymphoblasts, and lymphocytes are formed in large numbers in the loose meshes of the young connective tissue. Such aggregations of lymphocytes inserted on the course of a lymphatic channel break it up into a meshwork of tortuous, smaller channels interlacing through

valves which have been established early in development (Fig 412) By this time, also, the jugular and subclavian lymph sacs are in free communication. Extensions connecting the jugular lymph sacs with a superficial cervical plexus foreshadow the manner in which the cephalic and cervical lymphatic

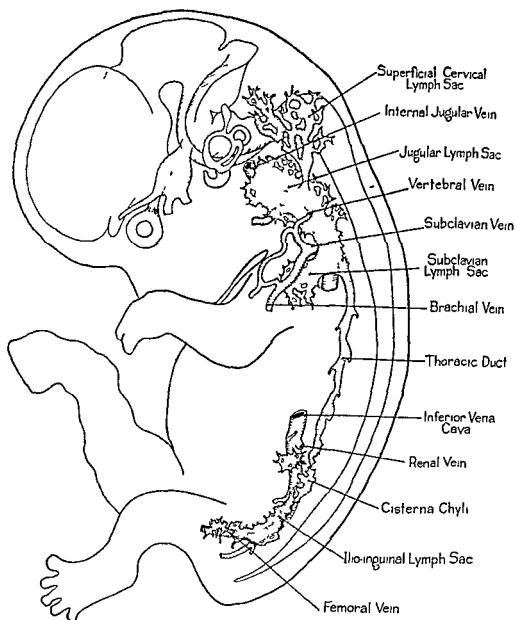


FIG 411 Lymphatic system of 30 mm human embryo (Redrawn after Sabin, in Keibel and Mall "Manual of Human Embryology," courtesy, J B Lippincott Co)

drainage will be established by way of the superior jugular channels. At its caudal extremity the thoracic duct is continuous with the cisterna chyli, which in turn receives mesenteric and ilio-inguinal tributaries (Fig 413). In embryos toward the close of the third month the arrangement of the channels which have thus been developed from the primordial lymph sacs already suggests the adult drainage pattern.

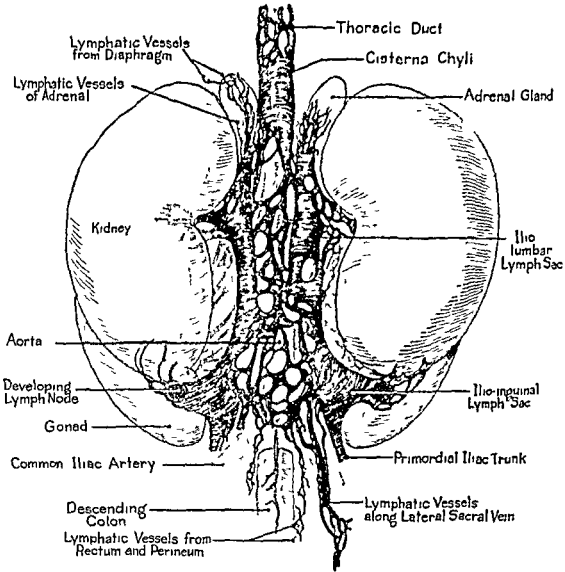


FIG 413 Dorsal view of injected 78-mm pig embryo to show cisterna chyli and developing ilio-inguinal lymphatic plexuses (After Reichert, Carnegie Cont to Emb, Vol 13, 1921)

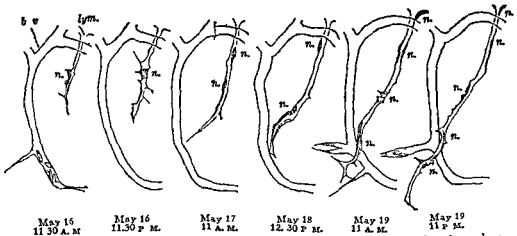


FIG 414 Diagrams showing successive stages in growth of a lymphatic vessel as studied in tail of a living tadpole (From Bremer-Weatherford 'A Textbook of Histology,' after Clark) Key b v, blood vessel, n, nucleus of endothelial cell of lymphatic vessel

